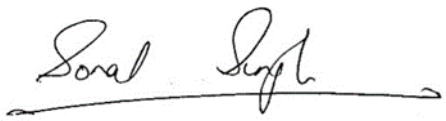
EXHIBIT C40

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF SONAL SINGH, MD, MPH



Date: November 16, 2018

Sonal Singh, MD, MPH

TALCUM POWDER PRODUCTS AND RISK OF OVARIAN CANCER
EXPERT REPORT

Prepared by

Sonal Singh, MD, MPH

University of Massachusetts School of Medicine

Nov 16, 2018

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I. INTRODUCTION AND SUMMARY.

I have been retained to review scientific evidence and analyze the epidemiological data and, based on these data and other relevant evidence, to provide my professional opinion about whether talcum powder products are causally related to ovarian cancer. I have used a weight of evidence approach in examining the causal relationship between talcum powder products and ovarian cancer. I have relied upon my own systematic review of the literature and the cumulative body of evidence as the basis upon which I provide my opinions. This included gathering all relevant data based on *in vitro*, animal, and human epidemiologic studies on this topic. Although the weight of my opinions is derived from findings published in the peer-reviewed literature, relevant unpublished documents are also noted when applicable. The individual studies were examined for both reliability and validity noting their strengths and limitations. The cumulative body of evidence was then synthesized and examined and weighed using a widely accepted organizing framework- the Bradford Hill approach. (1). Using these materials, my education, and my prior clinical and research experiences, I have employed the methods generally accepted by the scientific community that would be used to develop a peer-reviewed manuscript.

In summary, it is my opinion, to a reasonable degree of scientific and medical certainty, that talcum powder products, specifically here Johnson's Baby Powder and Shower to Shower, can cause ovarian cancer. This finding is based on the totality of the medical and scientific evidence from meta-analysis, and consistent findings of a statistically significantly increased risk in observational studies, evidence of retrograde migration and inhalation of talc, presence of known or suspected carcinogens in Talcum Powder Products, and inflammatory tissue response that initiates multiple pathways and biological mechanisms by which talcum powder products can cause ovarian cancer While these factors carry the most weight in my assessment, available data on the biological gradient of Talc exposure and ovarian cancer (dose response) also support my opinion.

II. BACKGROUND AND QUALIFICATIONS.

I am an Associate Professor in the Department of Family Medicine and Community Health and the Meyers Primary Care Institute, with a joint appointment in the Department of Quantitative Health Sciences at the University of Massachusetts Medical School, Massachusetts. I received

my M.B.B.S. (equivalent to M.D.) in 1998 from Patna Medical College, India. I then completed my internal medicine internship and residency in the Department of Medicine at the Unity Health Center, affiliated with the University of Rochester School of Medicine in 2005. Subsequently, I served on the Faculty as an Instructor of Medicine at Wake Forest University until 2007, and then as an Assistant Professor of Medicine in 2007. I received a joint appointment as an Assistant Professor of Epidemiology at Wake Forest University in 2008. While on the faculty at Wake Forest University, I obtained my master's in public health at Johns Hopkins University in 2008. I was an Assistant Professor in the School of Medicine at Johns Hopkins University as a recipient of the NIH Johns Hopkins Clinical Research Scholars Award in 2009. I held joint appointments in the Department of International Health and Health Policy and Managements and served as the Associate Director at the Center for Drug Safety and Effectiveness at Johns Hopkins University until 2016.

In my current position, I devote most of my professional time to epidemiologic research. I conduct clinical research with a focus on drug safety, evidence synthesis, and shared decision making. The major focus of my research is understanding the adverse effects of pharmacologic therapies. The remainder of my professional effort is dedicated to practicing general medicine and teaching activities. I have taught courses in systematic reviews, clinical epidemiology, pharmacoepidemiology, and the practice of internal medicine to medical students, interns, residents, and public health students at Johns Hopkins University and Wake Forest University. I have taught courses in clinical epidemiology and pharmacoepidemiology to researchers in the Bloomberg School of Public Health at Johns Hopkins University

I have served as an advisor to the World Bank, WHO International Agency for Research on Cancer and various pharmaceutical firms. I was part of World Health Organization International Agency for Research (WHO-IARC) panel which evaluated the carcinogenicity of various drugs and herbal products. (2). I currently serve as a member of the American College of Chest Physicians Guideline Panel. I have also been part of a panel that developed the PRISMA-HARMS (Preferred Item for Reporting Harm in Systematic Reviews and Meta-Analyses) checklist with an aim to improve the reporting of systematic reviews and meta-analysis of adverse effects. (3). My research has been funded by the Food and Drug Administration, the Agency for Health Care Research and Quality, the National Institute of Health and the Patient Centered Outcomes Research Institute. I am a recipient of numerous awards including the prestigious Johns Hopkins Clinical Research Scholars Award from the

National Institute of Health and the Tinsley R. Harrison Master Teachers Award at Wake Forest University School of Medicine. My systematic review on varenicline and the risk of cardiovascular events published in the prestigious Canadian Medical Association Journal was awarded the Best Research Paper of the year among hundreds of articles submitted to the Journal. I also serve as a peer reviewer for more than 50 journals and serve on the editorial board of prominent journals such as *BMJ Evidence Based Medicine*. I have reviewed grants for numerous federal and international organizations. I have conducted several epidemiological studies and systematic reviews and meta-analysis featured in prominent medical journals such as the *Journal of the American Medical Association* and the *British Medical Journal*. I have authored or co-authored more than 100 original peer-reviewed scientific articles and my work has been cited more than 13,000 times and my h-index is 48 [h number of papers which has been cited by others at least h times]. My work has been featured in *Science, Journal of the American Medical Association, British Medical Journal, and the Lancet*, as well as media outlets such as the NYTIMES, *Wall Street Journal* and *Washington Post*.

This background provides experise in the use of epidemiological research methods in diverse settings, and in the clinical practice of medicine, both relevant to the present scenario. I have charged a rate of $600.00 per hour in the preparation of this report. Attached as Exhibit A is a copy of my curriculum vitae.

III. PUBLICATIONS.

Below is a representative sampling of those articles published in leading medical journals such as *Journal of American Medical Association, Journal of American Medical Association-Internal Medicine,* and *British Medical Journal*. Please refer to my attached curriculum vitae for a complete listing of all publications.

- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone- A systematic review and meta-analysis. *Journal of the American Medical Association* 2007; 298: 1189-1195.
- Singh S, Loke YK. Furberg CD. Inhaled anticholinergics and the risk of major adverse cardiovascular events in Patients with Chronic Obstructive Pulmonary Disease: A systematic Review and Meta-analysis. *Journal of the American Medical Association* 2008; 300: 1439-1450. (CME Article in JAMA).

- Mills EJ, Wu P, Chong G, Ghement I, Singh S, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. Q J Med 2011; 104: 109-24.
- Singh S, Loke YK, Enright P, Furberg CD. Mortality Associated with Tiotropium Respimat® in Patients with Chronic Obstructive Pulmonary Disease- A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *British Medical Journal* 2011; 342: d3215.
- Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events with Varenicline: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Canadian Medical Association Journal* 2011; 1831359-66. (with an editorial by JT Hays. Varenicline for smoking cessation. Is it a heart breaker?)- Best Research paper of the year award.
- Singh S, Loke YK. Drug Safety Assessment in Clinical Trials: Methodologic Challenges and Opportunities. Trials 2012, 13: 138.
- Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Ovarian cancer Mellitus: A Population-Based Matched Case-Control Study. *Journal of the American Medical Association Intern Med*. 2013 25:1-6.
- Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. Collaborators: Stewart BW, Biggar RJ, Lachenmeier DW, Singh S, Tsuda H, Baguley B, Marques MM, Tseng CH, Knight TL, Beland FA, Betz JM, Carcache de Blanco EJ, Cunningham ML, Dunnick JK, Guo L, Jameson CW, Karagas M, Lunn RM, McCormick DL, Witt KL, Zhou S. Carcinogenicity of some drugs and herbal products. *Lancet Oncol*. 2013; 14(9):807-8.
- Zorzela, L., Loke, Y.K., Ioannidis, J.P., Golder, S., Santaguida, P., Altman, D.G., Moher, D., Vohra, S., Boon, H., Clark, J., Derry, S., Gallivan, J., Gardiner, P., Gøtzsche, P., Loder, E., Napoli, M., Pilkington, K., Shekelle, P., Singh S, Witt, C., Lasserson, T., Wu, T., Shamseer, L., Mulrow, C. PRISMA harms checklist: improving harms reporting in systematic reviews. *British Medical Journal* 2016;352: i157.
- Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 Nov;4(11):943-956.
- Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 Dec;130(12):1449-1457.

IV. STUDY DESIGN CONSIDERATIONS.

I will examine the strengths and weaknesses of the study designs that are relevant to the present scenario. Each of the study-types discussed below has its advantages and disadvantages. Every study is subject to biases and error; none is appropriate and feasible for every situation. Instead, the evidentiary value of each study must be assessed and weighed on an individual basis, and in the context of the totality of the body of literature or scientific studies.

IV.I Randomized controlled trials. In double blind randomized controlled trials (RCTs) both the investigator and the participant are blinded to treatment assignment. All characteristics whether known or unknown, are evenly distributed at random between the intervention and placebo arm. Thus, if there are differences in incidence of outcome, it can be inferred to be a consequence of the exposure itself (i.e. causative).

However, the prospective nature of RCTs also results in several significant drawbacks for effects that are rare and/or slow to develop, like ovarian cancer. In addition to the ethical difficulties of administering a substance that may be harmful, such as talcum powder products, it is difficult prospectively to ensure study-subject compliance over the decade-plus timeframes required to assess ovarian cancer risk, and obviously impractical to have researchers administer a daily perineal talc application to study subjects. Similarly, there is no mechanism by which to randomly assign participants for non-modifiable exposures or the event may be sufficiently rare, such as in the present case of ovarian cancer to be evaluated in a randomized trial. The definitive randomized controlled trial in which patients would be randomized to talcum powder products and/or placebo and measure the outcome of ovarian cancer would be ideal. However, such a randomized trial does not exist, and such a randomized trial would be unethical.[1] Then again, randomized clinical trials are not necessary to establish causal evidence of harm. For instance, there is no randomized trial which supports the causal role of smoking in lung cancer. As a result, to address this question, we must rely on other study designs including observational studies and their meta-analysis to draw inferences on causation. The preponderance of evidence we have on harms of products are derived from such epidemiological studies.

[1] Defendants here have admitted this fact. Deposition of Linda Loretz 562:14-563:6 (October 1, 2018) (4); Deposition of Joshua Muscat 408:21-410:20 (September 25, 2018) (5).

IV.II Systematic reviews and Meta-analysis. A systematic review and meta-analysis is a study design wherein systematic searches are carried out to identify studies reporting on a question of interest. Systematic reviews provide a high level of evidence when evaluating the effect of interventions. (6).

The meta-analytic point estimate represents the sum of evidence from all the included studies. When individual studies may be underpowered to detect an effect, meta-analysis of cumulative studies may allow one to distinguish whether the entire body of evidence supports the presence or argues against evidence of a causal association. Apart from the P-value as a measure of statistical significance, the confidence intervals are used to assess the statistical variability around the estimate. In a meta-analysis the studies are weighted by the sample size of included studies with larger studies contributing more weight to the final estimate. Studies are examined to determine whether the findings are clinically and statistically homogenous or heterogenous. Clinical heterogeneity includes any differences in populations and interventions. It is also important to evaluate statistical heterogeneity among studies included in the meta-analysis. (7). Although some amount of variation in individual estimates of treatment effect is expected by chance, the excess of variation which cannot be explained by chance alone is referred to as statistical heterogeneity. I^2 is used as a measure of *statistical heterogeneity*—a percent of variation due to heterogeneity compared to chance, the higher the value the more the proportion of statistical heterogeneity.

The different approaches to modelling data across studies may yield slightly different results. Fixed effects meta-analysis which assumes that all the studies are measuring the same effect yield tighter confidence intervals, whereas random effects meta-analysis which assume that studies are measuring different effects in the population yield more conservative effects. Random-effects models may be more appropriate when the amount of statistical heterogeneity is high. Some amount of heterogeneity is expected when the database includes observational studies.

However, it must be noted that while meta-analysis can overcome issues of limited statistical power and provide information on consistency or inconsistency of effects, one needs to carefully examine the individual studies for their limitations and susceptibility to bias and confounding.

Thus, for example, if a study is too short to detect the effect in question, then even a patient-level pooled analysis of several such studies will very likely fail to detect a true causal relationship, even when one exists. This is an illustration of why it is important to consider study design, bias, and confounding in weighing the results from both individual studies and their meta-analysis. Systematic reviews are also susceptible to various publication and funding biases which need to be considered in interpreting results.

Meta-regression in using summary or group level published data may be susceptible to ecological or group level biases and result in spurious conclusions. (8). As a result, it is not recommended to evaluate the association between treatment effect, such as the difference in the risk of ovarian cancer, and participant characteristics at the study level (e.g., mean age of all participants) using aggregate level data, (9) as these may be susceptible to group level or ecological biases. An individual participant pooled analysis in which investigators have access to the patient-level data, such as that by Terry et al. discussed below, (10) is considered of higher quality than meta-analysis of summary data and provides the ability to reliably assess the effect of other patient and outcome related variables.

Umbrella reviews and overviews of systematic reviews. An umbrella review systematically collects and reviews evidence from multiple systematic reviews and meta-analysis and allows integration of evidence from multiple systematic reviews and meta-analysis, (11) to offer a much broader view of the evidence landscape. Individual systematic reviews and/or meta-analysis included in an umbrella review or overview should be critically appraised for quality. The 11-item critical appraisal tool AMSTAR (Assessing the Methodological Quality of Systematic Reviews) is a reliable and valid tool which provides an assessment of the quality of included systematic reviews and meta-analysis in an overview. (12).

What is the precise causal question or the hypothesis being tested? One cannot interpret the scientific evidence without being precise about the causal question that is being addressed when evaluating the association between any exposure and an outcome in any epidemiologic study. An exclusively narrowly framed hypothesis (e.g., evaluating only one route of exposure such as using talcum powder on contraceptive diaphragm), (13) while disregarding other important and relevant routes and mechanisms of exposure, is inherently limited by design. Since we may not have a complete picture of the underlying mechanisms or the timings of risk of products at the

time of study design, it is even more critical that studies on safety evaluate all potential routes of exposure.

IV.III. Cohort and Case-Control Studies. There are several considerations in interpreting data from prospective or retrospective observational studies or case-control studies. However, it is important to consider issues of study design, random error, systematic error, bias, and confounding in the interpretation of data. Random errors are statistical fluctuations in the measured data due to the limitations of the measurement instrument. They may occur in both direction because of the inability to measure exposure and outcomes in precisely the same manner. There is also the possibility of measurement error in the measurement of outcome and exposure in both study designs. If the measurement error is non-differential, such misclassification of exposure or outcomes usually biases findings towards the null. Systematic errors, by contrast, are reproducible inaccuracies that are consistently in the same direction, often due to a problem which persists throughout the entire study and are difficult to correct.

Case-control studies involve subjects diagnosed with the disease at issue, such as ovarian cancer (the "cases"), and a suitable number of subjects without the disease (the "controls"). Exposure is ascertained retrospectively among both cases and controls. The results are then analyzed to see if there is an association between the exposure and the disease. In contrast, prospective cohort studies are study designs in which subjects with and without the exposure of interest are recruited and followed up in time for the development of outcomes. This study design establishes temporality wherein the exposure precedes the outcome. It is important to determine the latency and induction between the exposure and the disease to assess the duration of follow-up. As an example, a 12-month follow-up study to evaluate the association between exposure to smoking and lung cancer would be unlikely to demonstrate an increase in the risk of lung cancer.

There are several strengths to the case-control design including the ability to ascertain long-term exposure-outcome relationships, particularly important to the present scenario because ovarian cancer develops over many years. Once cases and controls have been established, one can evaluate the association between multiple exposures and outcomes. In contrast, prospective cohort studies may be limited by the short-duration of follow-up which may be insufficient to ascertain the effect of exposure on long-term outcomes and bias their findings towards the null. Secondly, for relatively rare diseases, such as ovarian cancer, case-control studies are more

efficient. Because we are looking at the incidence of disease between the two arms of a study, a cohort study may have limited statistical power regardless of the actual number of subjects enrolled if the number of cases is small. For example, the Nurses' Health Study recruited almost 80,000 participants for only 307 cases of ovarian cancer. (14).

Both study designs are susceptible to selection bias when the selection of the participants into the study (or their likelihood of being retained in a cohort study) leads to a result that is different from the result had we enrolled the entire target population. In other words, the exposure-outcome relationship in controls or cases may be different from the target population. This can arise due to selection of controls not representative of the target population, non-response that is related to exposure and outcome, or differential loss to follow-up in a cohort study related to exposure and outcome status. Selection bias can bias findings either away from the null or towards the null.

Case-control studies, by their design, are generally not blinded and are also susceptible to bias as a result. They are also susceptible to recall bias, i.e. the concern that subjects with the disease may be more diligent in recollecting past uses. However, the degree of recall bias will depend on the type of exposure with chronic daily long-term exposures, such as talcum powder product use, being less likely to be subject to recall bias than intermittent short-term exposures. In contrast, prospective cohort studies in which subjects are recruited and then followed up for the development of outcomes are less susceptible to recall bias.

In addition, there is the issue of what may be called "behavior change" bias in cohort studies which may also bias their findings towards the null if exposure is only ascertained at baseline and not updated during follow up. This bias towards the null reduces the apparent effect of the exposure on the outcome. For example, if the subjects accurately report their talcum powder product use (or lack there-of) at baseline, but there is no follow-up, then the "ever" users' status will still be correct at the end of the study, because once having used talc, their "ever" status cannot change. This will not be true, however, of the "never" users; if they subsequently use talc, then without follow-up, their status will still be incorrectly recorded as "never." If there is a true causal connection, some ovarian cancers caused in the "never" category will, in fact, belong in the "ever" category, potentially biasing the study towards the null. Cohort studies are also susceptible to attrition bias and efforts should be used to minimize loss to follow-up. The main strengths of cohort studies are that if an effect (after adjusting for other confounding

factors) is found despite these biases towards the null, then it is more likely to be a causal relationship; the limitations being that they are less sensitive to determining a causal relationship. Case-control studies are based on past behavior and are not affected by this bias. Cohort studies are also susceptible to several prevalent user biases including potential bias due depletion of susceptibles. (15). A cohort study evaluating the association between talc use and ovarian cancer which limits the analysis to prevalent users (rather than new users), may largely be composed of survivors of the early effect of talc exposure on ovarian cancer, since new users who developed ovarian cancer after talc exposure may be ineligible for inclusion. This will potentially bias the estimates towards the null.

One important distinction to note is between risk factors for the disease and confounders. (16). A risk factor is an exposure which may explain the development or cause of disease in the population. These could be potentially modifiable or non-modifiable risk factors such as genetic risk factors. Confounding represents a special case of bias that results when the relationship between the risk factor -disease relationship is altered. A variable is considered a confounder only when ALL three criteria are present: a) the confounder is associated with the exposure in the population; b) the variable is related to the disease in the population; and c) the variable is not a link in the causal pathway to the disease. Risk factors that do not meet all the above criterion are not considered confounders of the exposure-outcome relationships (and thus may not require adjustment in the analysis).

Observational studies may also be susceptible to unmeasured confounding. Importantly, the potential for confounding does not mean that such a confounding exists. To address bias, confounders of the disease-outcome relationship need to be adjusted for in the analysis of epidemiologic studies. The methods for adjustment for known confounders include regression or propensity score methods. In establishing the effect of any exposure on an outcome it is important to disentangle the direct effect of an exposure of an outcome vs the indirect effect because of some mediators. The strength of association, in and of itself, does not denote whether a risk factor causes the disease. It is reflective of the background rate of the disease in the population and the relative risk of other competing risk factors. When the strength of association is weak, restricting the disease to a low risk population with low background rates of the diseases will magnify the association due to lack of competition among risk factors. (16)

One must be careful in interpreting data from subgroup analysis, such as analysis of various dose categories or age or ethnic groups, such as the case here with pre-menopausal women vs post-menopausal women or subgroup of women stratified by age, sex and ethnicity. The results of tests of interaction are important in interpreting data from such studies. If the test of interaction is not significant, this suggests that there is a lack of significant difference between the two groups. However, such subgroup tests can be underpowered because of reduction in sample size. Additionally, while a study may be internally valid it may not be generalizable to participants in the overall population beyond those included in the study. As an example, the cohort study of post-menopausal women reporting a non-significantly increased risk of ovarian cancer with genital talc use may not be generalizable to premenopausal women. (17). Despite the limitations noted above, most of our knowledge of the adverse effects of therapies has been derived from observational studies, since randomized controlled trials are not practical for several agents and rare outcomes.

It is also important to draw attention to the proper interpretation of P-values, confidence intervals and statistical significance. (18). I have followed the general principles laid out by the American Statistical Association on the interpretation of P-values and statistical significance. P-value can only indicate how incompatible data are with a statistical model. P-values do not indicate the probability that the studied hypothesis is true or the probability that data were produced by random chance alone. A P-value does not measure the size of an effect or the importance of a result and undue reliance should not be placed on whether a P-value passes a specific threshold. Full reporting and transparency are needed for interpretation of results. Confidence intervals (CI) measure statistical significance, (19) and indicate the precision and degree of uncertainty associated with a sample statistic. A 95% CI means that if we used the same sampling method to select different samples and computed an interval estimate for each sample, we would expect the true population parameter to fall within the interval estimates 95% of the time. CIs that remain elevated above 1 for relative risks (RRs) or odds ratios (ORs) are considered statistically significant. A narrow CI indicates a relatively higher level of precision. Non-overlapping CIs across two studies suggest a statistically significant difference between the study findings, whereas overlapping CIs may suggest consistent results. Thus, it is not necessary, and it is highly unlikely to have identical point estimates across studies to establish the presence of a consistent exposure-outcome association.

V. EPIDEMIOLOGY AND PATHOGENESIS OF OVARIAN CANCER.

Ovarian cancer is the most lethal gynecologic cancer in women. It is the leading cause of cancer death among gynecologic cancer in the US and the fifth most common cause of cancer with more than 14,000 deaths per year. The incidence is 11.4 cases per 100,000 women per year, with a mortality rate of 7.4 deaths per 100,000 women. (20). Approximately 1.3 percent of women will be diagnosed with ovarian cancer at some point during their lifetime. Approximately 22,400 new cases of ovarian cancer would be diagnosed in the US in 2017 with 14,080 deaths. (21).

Most women are diagnosed at an advanced stage of the disease and it is usually asymptomatic but may present as abdominal distention, bloating, and in a minority of cases vaginal bleeding. The prognosis is relatively poor when it presents at the advance stage where therapeutic options including chemotherapy offer little benefit. As discussed in more detail in Section X below, inflammation is known to play an important role in the pathogenesis of ovarian epithelial cancer through a mechanism of cell proliferation, oxidative stress DNA damage and gene mutations.

VI. WHAT CONSTITUTES COSMETIC TALCUM POWDER PRODUCTS?

- While I will examine the evidence of talcum powder products and their causal association with ovarian cancer, ascertaining what constitutes "talcum powder" it is important to emphasize that Talcum powder cosmetic products are not "pure talc." The evidence I reviewed demonstrates talcum powder products contain asbestos, fibrous talc, heavy metals such as cobalt, chromium, nickel, and various fragrance chemicals (22)(23). This report evaluates the risk of ovarian cancer associated with talcum powder products and its constituents. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within.

- Talc is a naturally occurring mineral and its chemical composition is hydrous magnesium silicate with a chemical formula of $Mg_3Si_4O_{10}(OH)_2$. In its natural form, talc may contain asbestos, also a naturally occurring silicate mineral, with a different crystal structure. Both talc and asbestos belong to the family of silicates that may occur in fibrous form, which is known to cause cancer. The structure of talc is characterized by a hexagonal sheet arrangement of silicon oxygen tetrahedral groups in a common plane. This results in a double-sheeted structure where the sheets are held together by weak van der Waals bonds. Talc consists mostly of these plate-

like structures ("platy talc") but talc can occur in fibrous form. Talc fibers are like asbestos fibers in size and shape. (22, 24).

- Despite claims that talcum powder products manufactured after the mid-1970s were "asbestos free," published articles, internal company documents, and testing of historical samples I reviewed demonstrate that talcum powder products can contain asbestos and other carcinogenic constituents as discussed below. For example, talc powders from national and international markets were analyzed by Paoletti et al. in a 1983 study to assess fiber content. (25). Samples of talc powders demonstrated fiber contents up to 30% of total particles. About half of the talc powders revealed the presence of asbestos. In some samples, a very high level of asbestos was revealed. (25). Consistently, the 1991 Blount study also found asbestos in cosmetic talcum powder. (26). In a recent deposition, the author of the 1991 study testified she had detected specifically in Johnsons and Johnsons baby powder. (27).

- Although the FDA conducted a survey of talc manufacturers in 2009-2010 and found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc, (28) the results were limited; only four out of nine talc suppliers submitted samples, and the number of products tested was low. The failure to detect asbestos could either be due to the technique used or the use of a non-representative sample. The FDA itself noted the study could not "prove that most or all talc or talc-containing cosmetic grade products currently marketed in the United States are likely to be free of asbestos contamination." (29).

- I reviewed Longo et al.'s report from August 2017 where he tested 30 bottles of Johnson's Baby Powder. (30). They found 17 samples contained detectable amounts of asbestos. They also found half of the samples contained fibrous talc. I also reviewed two additional reports from Dr. Longo where he found fibrous talc and asbestos in Johnson's Baby Powder. (31, 32). I reviewed the depositions and exhibits of Dr. John Hopkins, corporate representative for Johnson and Johnson, who testified to numerous positive tests for asbestos and fibrous talc. (33).

- In a recent report, Longo et al. (34) estimates that 37 out of 56 random samples (66%) of bottles of talcum powder products tested contain asbestos, which indicates that approximately 2 out of 3 bottles of talcum powder containing products are contaminated with asbestos. Talcum powder products are generally used by women habitually for months or years, rather than a

single application or a single bottle of use. Each successive use of a bottle of talcum powder product_by an individual further accentuates the cumulative probability of their exposure to asbestos, beyond the probability conferred by the use of a single bottle. I reserve the right to supplement my report in order to estimate this probability of exposure to asbestos through habitual use of talcum powder products contaminated with asbestos, once the analysis of additional samples of talc is complete. Longo et al. also estimates that 41 of 42 random samples of bottles of talcum powder products tested contain fibrous talc. I reserve the right to supplement my report in order to estimate this probability of exposure to fibrous talc through habitual use of talcum powder products contaminated with fibrous talc, once the analysis of additional samples of talc is complete.

- I also reviewed the deposition and exhibits of Julie Pier, corporate representative for Imerys Talc America, Inc., who testified to numerous positive tests for asbestos and heavy metals between 1985 and 2002. (35).

- My review of monographs published by the International Agency for Research on Cancer (IARC) show that asbestos is a well-established carcinogen and unequivocally known to cause several cancers including mesothelioma of the lung, larynx, and ovarian cancer. (36). Overall, the International Agency for Research on Cancer Working Group classified asbestos compounds as "carcinogenic to humans" (Group 1) in 2012. (36, 37). IARC has also concluded that talc including asbestiform fibers grown in an asbestiform habit - commonly termed "fibrous talc" - is "carcinogenic to humans" (Group 1). (38).

- I also reviewed documents demonstrating talcum powder products may contain heavy metals such as chromium, nickel, and cobalt. (22). Asbestos, chromium, and nickel were all classified as a Group 1 carcinogens by IARC. (36) Cobalt is also present in talcum powder products and classified by IARC as a Group 2B carcinogen.

VII. SUMMARY OF OPINIONS.

1. **Statistical Significance**. There is a statistically significant increased risk of ovarian cancer with talcum powder products as demonstrated by most meta-analyses to date. (10, 39-42). Although a flawed analysis conducted limited to the use of talc dusted diaphragms and ovarian cancer conducted on behalf of the manufacturer reported an excess risk which was not

statistically significant, (13) it had several data extraction errors and was of lower methodological quality. (43). Several independent meta-analysis by academic researchers, some of which include individual participant data, (10) and the most recent meta-analysis reported a statistically significantly increased risk of ovarian cancer associated with perineal talc use, (42) rendering the previous findings of Huncharek et al obsolete. The studies of the highest rated methodologic quality as shown in **Table 1** which provides a methodologic grading of the quality of the included systematic reviews using the AMSTAR checklist have reported a statistically significantly increased risk of ovarian cancer associated with genital talc use. (10, 41, 42). See Section IX.IV for a summary of findings from epidemiological studies.

2. **Consistency and Replication**. These findings of a statistically significantly increased risk of ovarian cancer with talc use have been consistently replicated by several independent investigators in different population, and different settings across different data sources using different study designs. These slight differences in magnitude of risk reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time. The meta-analysis of case-control studies has consistently shown a statistically significantly increased risk, whereas the meta-analysis of cohort studies has also shown an excess risk, (42) which failed to reach statistical significance, due to inadequate statistical power and low number of events; but the confidence intervals of results between the two study designs overlap providing evidence of consistency. The number of ovarian cancers in the case-control studies exceeds the number of ovarian cancers in the cohort studies by several fold. (42).

3. **Strength of Association**. The cumulative strength of association for the increased risk of ovarian cancer associated with talcum powder containing products is significant and ranges from 30 % to 60% %. The strength of association is similar to estimates of other established carcinogens (e.g., 24 % increased risk of lung cancers in non-smokers exposed to environmental tobacco smoke) (44), hormone replacement therapy and breast cancer (RR 1.33, 95% CI: 1.24-1.44) (45), particulate matter and lung cancer (PM2.5: RR 1.09, 95% CI: 1.04, 1.14 and PM10: 1.08, 95% CI: 1.00-1.17). (46). Beyond carcinogens, there are well established examples of causal associations in epidemiology, such as in the case of particulate matter and myocardial infarction, where the statistically significant excess risks are in the order of even less than a percent (carbon monoxide: 1.048, 95% CI: 1.026-1.070; nitrogen dioxide: 1.011, 95% CI, 1.006-1.016; sulfur dioxide: 1.010, 95% CI: 1.003-1.017; PM(10): 1.006, 95% CI: 1.002-1.009; and PM(2.5): 1.025, 95% CI: 1.015-1.036 and ozone: RR 1.003, 95% CI: 0.997-1.010; P = .36). (47).

4. **Exposure-Response Assessment.** The assessment of exposure–response or biological gradient is hindered by the difficulty in quantifying talcum powder use usually collected by

self-reported data (frequency, amount, and duration), timing and patterns of use (e.g., douching), and other individual factors (e.g., co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. As discussed in the dose-response summary of epidemiological studies below, some studies have measured the frequency of exposure, others the duration of exposure with few studies measuring the combined duration and frequency or intensity of exposure. (48). It is important to interpret the exposure-response data in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer through alteration of the redox state in epithelial ovarian cancer cells, (49) and a monotonic dose-response curve may not accurately reflect this mechanism of development of ovarian cancer mediated via inflammation and alterations in redox states. Some epidemiologists have argued that it is difficult to know how dose-response should be modelled and it is unclear why nature would mandate a monotonic dose-response gradient. (50). Although it is difficult to know how to model the talc-ovarian cancer exposure-response assessment, it is possible that an agent which accelerates the development of cancer could account for threshold effects rather than monotonic dose-response effect. Despite these challenges, I address studies which have shown evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 57). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis reported an increased risk with >3600 lifetime applications compared to <3600 lifetime applications of perineal talc based on data from case-control studies. (42). A limited number of studies have shown no evidence of dose-response either with increased frequency or duration of exposure. (58-60).

5. **Retrograde Migration of Talc and Routes of Talc Exposure.** Talcum powder particles can migrate to the fallopian tubes and ovaries. (61-63). Talc and/or other constituents have been detected within the ovaries of women who report perineal talc use, (64) and found deeply embedded within ovarian tumors. (62, 65). Talc has also been reported in the lymph nodes which could occur through migration absorption or inhalation with transport through the lymphatic system. (66). Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of "measurable quantities of talc" in unrelated monkey models, (67) the timing and techniques of assessment and intraspecies differences could not completely rule out migration of talc particles. Furthermore, supportive evidence for migration comes from the findings of a decreased risk of ovarian cancer with tubal

ligation and hysterectomy, (62) evidence of migration of other particles such as starch. (68). The FDA concluded that the "potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable." (69). A secondary route of exposure is inhalation. (36, 70).

6. **Multiple Biological Mechanisms of Talc Induced Ovarian Cancer.** Although not an absolute requirement for demonstrating causality, there is strong evidence that talcum powder products can induce ovarian cancer through established biological mechanisms (Section X). (39, 49, 71, 72). Inflammation plays a leading role in ovarian cancer and talc has pro-inflammatory effects; it also induces alterations in redox potential and pro-oxidant effects. (49) In ovarian cells talc has been shown to increase proliferation, increase neoplastic transformation and increase reactive oxygen species in the ovarian cells. (71). Talc has also been shown to be mutagenic in human ovarian epithelial cells through increased activation of gene activating transcription factors. Finally, the presence of asbestos and other Group 1 carcinogens likely contributes to the carcinogenicity of talcum powder products, and provides biologic plausibility for the consistent and significant increased risk seen in the epidemiologic studies on Talc and Ovarian cancer.

VIII. METHODS FOR THE OVERVIEW OF SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES OF GENITAL TALC USE AND OVARIAN CANCER.

I conducted an overview of systematic reviews and meta-analysis of observational studies of genital talc use and ovarian cancer. I included systematic reviews regardless of the performance of quantitative synthesis as meta-analysis may occasionally not be performed for data from observational studies. To inform the causal question, I also evaluated additional studies which provided evidence on the causal question of whether talcum powder products induce ovarian cancer. I critically appraised the meta-analysis using the 11- item AMSTAR (Assessing the methodologic quality of Systematic Review) checklist for systematic reviews and meta-analysis. (12) The individual epidemiological studies were also evaluated and summarized for their key strengths and limitations.

VIII.I. Systematic search. I performed an initial systematic search of Scopus and PubMed with the following search terms on June 12, 2017:

Pubmed: ("talc"[MeSH Terms] OR "talc"[All Fields]) AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All

Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])

Scopus: (TITLE-ABS-KEY (talc) AND TITLE-ABS-KEY (ovarian AND cancer)

VIII.II Eligibility Criteria. I included and considered epidemiological studies, including case-control studies, cohort studies and systematic review and meta-analysis which reported on the association between talc and ovarian cancer. I searched the references of included studies and citing articles to find additional original articles. I also included in vitro, animal, and human epidemiologic studies that reported data that either support or refute the role of talc in the development of ovarian cancer. I excluded duplicate articles identified in the two databases, articles with no original data, narrative reviews, commentaries and opinion pieces , and citations not relevant to the present scenario. The title and abstracts of each manuscript were reviewed to identify potential studies for inclusion in this report. I also searched the reference of included studies to find relevant citing articles. New studies were identified after evaluating citing articles. I reviewed the full length of each of these manuscripts and provide a summary of their key findings below.

IX. RESULTS.

The results of the initial search yielded 273 citations. I included 9 studies in the section on overview of systematic reviews and meta-analysis. (10, 13, 39-42, 57, 73, 79). I also assessed the 29 case-control studies, (48, 51-60, 62, 66, 75-91) and 3 cohort studies (14, 17, 92-93). The list of excluded citations is shown. The difference in the citation count of included and excluded articles largely reflects excluded duplicate articles retrieved from the two databases. I also evaluated several studies (36, 37, 49, 64-68, 72, 94-109) which reported on the biological mechanisms that supported or refuted the causal association between talcum powder products and ovarian cancer.

IX.I. Overview of Systematic Reviews and Meta-analysis. Three meta-analysis were not preceded by a systematic search (57, 73, 79). There were 4 systematic reviews and meta-analysis which evaluated the link between perineal talc use and ovarian cancer (39-42) using summary data, while an individual participant data analyses pooled data from case-control studies in the Ovarian Cancer Consortium (10). Another systematic review and meta-analysis analysis conducted on behalf of the manufacturer only evaluated the use of cosmetic talc on

contraceptive diaphragms and ovarian cancer (13) and was not directly relevant to the causal question of genital talc use and the development of ovarian cancer, but was critically evaluated for strengths and weaknesses. The results of the methodologic assessment of each of these using the AMSTAR checklist is summarized in the Table 1. Two meta-analysis (13, 40) are of poor methodological quality. Regardless, the findings of older meta-analysis have been superseded given the publication of new meta-analysis. (41, 42).

1. In 1992, Harlow et al. combined crude odds ratios from their case-control study, discussed below with 5 pre-existing existing case-control studies (79) to evaluate the association between perineal talc exposure and ovarian cancer. The studies included 1106 cases and 1756 controls, with talc exposure reported among 50.7% of cases and 46.9% of controls. Using crude odds ratios from the individual studies, perineal exposure to talc was associated with a statistically significantly increased risk of ovarian cancer (OR 1.3, 95% CI: 1.1-1.6). Major limitations include the lack of a systematic search methodology.

2. A 1995, meta-analysis by Gross and Berg (39) was conducted on behalf of the manufacturer Johnson and Johnson. A search of PubMed issuing the terms "ovarian cancer" and "talc or cosmetic" identified 9 case-control studies and reported a statistically significant increased risk of ovarian cancer in both the crude odds ratio (1.27, 95% CI: 1.09-1.48) and adjusted odds ratio (1.31, 95% CI: 1.08-1.58). They also examined the odds ratio by tumor type and notes that all the analyses produced relative risks greater than 1 with confidence intervals that exceeded 1. Despite the statistically significantly increased risk seen in analyses, the authors concluded that the *"literature does not unequivocally support the hypothesis…. But [does] suggest the possibility of an increased risk of ovarian cancer due to perineal talc use."* The description of study procedures was incomplete, and the search strategy was limited. The study was supported in part by the manufacturer.

3. Cramer et al. 1999 combined crude odds ratio data from their case-control study with pre-existing case-control studies in a meta-analysis of 14 total case-control studies, (57) and reported a statistically significant OR of 1.36 (95% CI: 1.24-1.49). The tests for statistical heterogeneity were not significant (p=0.085). Limitations include the lack of a systematic search.

4. Huncharek, for his 2003 publication, conducted a meta-analysis of 16 studies including 11,933 subjects. (40). They searched MEDLARS, Embase and Cancer Lit databases using search term "talc exp ovarian neoplasms." They excluded studies on borderline tumors or those which did not report on types of perineal exposure (dusting vs sanitary napkins). The meta-analysis was conducted using adjusted measures of effect using the inverse variance method. It included 15 population-based and 1 hospital-based study and excluded the 1983 Hartge study. (76). The pooled analyses yielded a significantly increased risk of ovarian cancer (RR 1.33, 95% CI: 1.16-1.45) associated with the perineal use of talc without evidence of statistical heterogeneity. Seven studies reporting on the number of talc applications per month were evaluated where the highest risk category (RR 1.21, 95% CI: 1.00-1.45) and lowest risk category (RR 1.83, 95% CI: 1.55-2.15) reported an increased risk. In sensitivity analyses, hospital-based studies showed no statistically significant excess risk between talc use and ovarian cancer risk, i.e., RRs 1.19 (95% CI: 0.99-1.41) versus population-based studies which showed an increased risk (RR 1.38, 95% CI: 1.25-1.52), despite the proportion of controls using talc being similar across the two designs. The confidence intervals were overlapping suggesting that the findings were consistent. Recent updated meta-analysis discussed below report similar estimates from hospital and population based studies. (42). The RRs were relatively stable even after exclusion of the single cohort study or limiting the analysis to studies that controlled for body weight and BMI. The authors stated that the association between talc use and ovarian cancer could also be attributed to exposure misclassification among prevalent cases or side effects of treatment such as radiotherapy and chemotherapy which may predispose to talc use ("reverse causality"). Study limitations include the inability to conduct meaningful dose-response analysis because only nine of the 16 studies provided data on dose-response, with substantial differences in dose stratification levels among these studies.

5. Langseth reported on a meta-analysis of 20 case-control studies and one cohort study in 2008. The various case-control studies provided a significant excess risk (10 studies) and non-significant excess risk in 10 studies. (73). The prospective cohort study reported no association between cosmetic talc use and all types of ovarian cancer combined but showed evidence of an increase in serous tumors. The hospital-based case-control studies reported a pooled OR of 1.12 (95% CI: 0.92-1.36) and population-based case-controls studies reported a pooled OR of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using the fixed effects model was 1.35 (95% CI: 1.26-1.46).

6. Terry et al conducted an individual participant pooled analysis of eight case-control studies was conducted by the investigators for the Ovarian Cancer Consortium. (10). Genital powder use was defined as any powder use (talc, cornstarch, deodorizing) applied directly or indirectly (with sanitary pads, tampons or underwear) to genital, perineal or rectal area. Criteria for exposure varied from ever use to one year or longer. Women who reported both genital and non-genital powder use were considered genital users. Cumulative exposure was calculated by multiplying months of use by frequency of use. Never users and women who reported non-genital powder use were considered as the reference group. Analyses were adjusted for potential confounders such as age, duration of contraceptive use, parity, tubal ligation history, BMI and race/ethnicity. Family history of breast and ovarian cancer was not included in the final model. Genital powder use was reported in 25% of controls and 31% of cases. The rates of genital powder use varied widely between studies ranging from 15-45% in the control group. Ever regular uses of genital powder reported a statistically significantly increased risk of ovarian cancer (OR 1.24, 95% CI: 1.15–1.33) compared to non-users. There was no evidence of heterogeneity in the studies regardless of the reference group ($P_{heterogeneity}$=0.61). Results were similar when the reference group included those with genital powder use and never users. Risk was elevated for various histologic subtypes of ovarian cancer including invasive serous (OR 1.20, 95% CI: 1.09–1.32), endometrioid (OR 1.22, 95% CI: 1.04–1.43), and clear cell (OR 1.24, 95% CI: 1.01–1.52) tumors, and for borderline serous tumors (OR 1.46, 95% CI: 1.24–1.72). There was an increased risk of all nonmucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder use compared with nonuse: (OR_{Q1} 1.18, 95% CI: 1.02–1.36; OR_{Q2} 1.22, 95% CI: 1.06–1.41; OR_{Q3} 1.22, 95% CI: 1.06–1.40; OR_{Q4} 1.37, 95% CI: 1.19–1.58). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis (P_{trend} < 0.0001), no significant trend was seen when analyses were restricted to ever users (P=0.17). After excluding those with tubal ligation or hysterectomy, the results were similar. Restricting analysis to applications before tubal ligation made no substantive difference. There was an evidence of interaction by BMI, with the risk being higher for women with BMI < 30 kg/m^2 (OR 1.28, 95% CI: 1.17-1.39) than women with BMI ≥ 30 kg/m^2 (OR 1.14, 95% CI: 0.98-1.32; $P_{interaction}$=0.01). There was no evidence of interaction by tubal ligation, parity, endometriosis or post-menopausal status. The association was similar for women who used powder during varying time periods (1952-1961; 1962-1972; and after 1972). The strengths of this meta-analysis include the use of individual participant data, which allowed them to conduct dose-response analysis and analysis by histologic subtype. The lack of statistically significant evidence on non-

mucinous cancer could be attributed to the low number of users, or talc may not be relevant to these tumor types which have different biological mechanisms. The limitations include the definition of exposure as genital powder user varied from ever user, ever regular user to powder use for at least 6 months or at least 1 year in the studies.

7. Berge et al. 2018, a meta-analysis of 27 studies (41) (24 case-control studies and 3 cohort studies) was conducted according to the Preferred Item for Reporting of Systematic Reviews and Meta-Analysis Guidelines. (110). The authors searched multiple databases including Pubmed, Embase and Scopus. They examined the citations independently and in duplicate. They rated the studies using the New Castle Ottawa scale for study quality. They conducted meta-regression for duration (RR for every 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency) for studies reporting at least three categories of duration or frequency after excluding the non-exposed category. Dose-response analysis was conducted using two methods. Study specific slopes were estimated from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model. The study specific estimates were pooled in a single meta-analysis in the second method. Six of the case-control studies were hospital-based and the remainder were population-based. Most of the studies were conducted in North America and Europe. They reported a statistically significant increase in risk of developing ovarian cancer with talc use (adjusted RR 1.22, 95% CI: 1.13-1.30). A statistically significant risk was seen in the case-control studies (RR 1.26, 95% CI: 1.17-1.35), whereas the excess risk in the cohort studies did not reach statistical significance (RR 1.02, 95% CI: 0.85-1.20; $P_{heterogeneity} = 0.007$). There was no difference between results for borderline (RR 1.27, 95% CI: 1.09–1.44) and invasive ovarian cancer (RR 1.20; 95% CI: 1.08–1.31). There was a trend in RR with duration and frequency of genital talc use and suggestion of dose-response. There was a statistically significant risk for only serous carcinoma (RR 1.24, 95% CI: 1.15–1.34) and no other histologic subtypes ($P_{heterogeneity}$ between histologic types was 0.04). Use of talcum powder in the "early" period showed increased risk of ovarian cancer (RR 1.18, 95% CI: 0.99–1.37). The use in the "late" period was higher (RR 1.31, 95% CI: 1.03–1.61; P-value for test for heterogeneity between the groups of studies was 0.37), arguing against the hypothesis that a higher risk would be seen only among those with earlier exposure during time-periods in which talcum powder was reported to contain asbestos. The cut-off points varied between studies was variable between 1970 and 1980. Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR 1.00: 95% CI: 0.84–1.16, and RR 0.75, 95% CI: 0.63–0.88, respectively).

Stratified analysis based on the adjustment for confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/ education, BMI) found no evidence of heterogeneity. Meta-regression using the two different approaches yielded similar results. Based on the two-step approach, a 10-year increase in genital talc use was associated with a RR of 0.97 (95% CI: 0.82–1.12; nine studies reporting on duration), whereas the RR for an increase of one application per week was 1.03 (95% CI: 0.82–1.25; five studies reporting on frequency). There was no evidence of publication bias on visual inspection of funnel plot and the Egger test (P=0.7), with the cumulative meta-analysis reporting stabilization RR of in the range of 1.20–1.25. Stratified analyses conducted did not suggest the possibility of residual confounding (i.e, higher adjusted estimates than unadjusted estimates).

There are some limitations to the analysis. While the role of selection and recall bias is a possibility, given higher estimates reported from recent studies, such biases should account for increase in recall for all histologic cancer subtypes and not just serous ovarian cancer. Importantly, the dose-response analyses analyzed duration and frequency separately and not the intensity of exposure (duration combined with frequency) or cumulative exposure to talc and the exclusion of the reference category from the dose-response curve diminished the power of the dose response analysis to detect any threshold effects.

8. Penninkilampi, et al. 2018 (42), the most recent and comprehensive meta-analysis which focused on studies with greater than 50 cases of ovarian cancer also reported on data from 26 case-control studies (13,421 cases and 19,314 controls) and 3 cohort studies (890 cases). The study was also conducted according to the PRISMA protocol and included a search of multiple databases (MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials) and LILACS. They also evaluated the quality of studies using the Newcastle Ottawa Scale. They also evaluated long term talc use in which OR were extracted for group with the longest duration of exposure compared to controls, if there was a minimum of 10 years of talc exposure. Lifetime applications within each study were divided into < 3600 lifetime applications (equivalent to less than 10 years) and >3600 applications or more than 10 years of exposure. The number of lifetime applications is a better marker of intensity of exposure compared to duration or frequency of exposure alone. They assessed publication bias using the failsafe method where the failsafe number is the number of studies missed to nullify the findings of meta-analysis.

This was a well-conducted analysis and some strengths and limitations are notable. They found all studies to be of reasonable quality and did not exclude studies based on study quality. None of the analyses in this review had statistically significant heterogeneity except for non-perineal application arguing for the consistency of estimates. Any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, 95 % CI: 1.24-1.39). Greater than 3600 lifetime applications were more associated with ovarian cancer than lifetime applications of less than 3600, although risks were significantly elevated in both groups. While the case-control studies reported a statistically significantly increased risk of ovarian cancer (OR 1.35, 95% CI: 1.27-1.43), the cohort studies reported an increased risk which was not statistically significant (OR 1.06, 95 % CI: 0.90-1.25).

9. Meta-analysis on Talc-Dusted Diaphragms and Ovarian Cancer. Another meta-analysis of 9 case-control studies by Huncharek et al. (13) reported on exposure to talc dusted diaphragms and ovarian cancer. On one hand, the authors dismissed the "talc hypothesis" for potential carcinogenicity, but then argued that talc dusted diaphragms was a more "intuitive model" for testing whether talc exposure increased the risk of ovarian cancer without any biological evidence (or references) to support this intuition. They searched MEDLARS, Cancer Lit and Current Contents. They included 9 studies and the pooled analyses yielded an excess risk of ovarian cancer which was not statistically significant (RR 1.03, 95% CI: 0.80-1.33). Exclusion of the study in which exposure to dusted diaphragms was assumed rather than measured further elevated the OR, which was not statistically significant (OR 1.12, 95% CI: 0.84–1.48) similar to a non-significant elevation in OR after the exclusion of the studies not published as full research articles.

This meta-analysis was flawed for several reasons. The most important limitation was its exclusive focus on talc powder dusted diaphragms as the route of exposure which could not inherently address the causal question of whether genital talcum powder dusting is associated with increased risk of ovarian cancer. As a result of this narrow hypothesis, they excluded several available studies that reported a statistically significant excess risk of ovarian cancer with perineal talc use. Several methodological flaws include the exclusion of the lowest category of exposure for some studies, (51) data extractions errors for others (56), and inclusion of ineligible studies that did not disaggregate data between talc and cornstarch users. (77) The study was by Johnson & Johnson and Luzenac America and was of poorer methodological quality than those conducted by their academic counterparts (43). As a result of these serious methodological

flaws, and the publication of several newer, higher quality meta-analysis with updated data, (10, 41, 42) the findings of this study have been superseded.

It is important to note here that while the AMSTAR checklist evaluates the methodologic quality of systematic reviews, several studies shown below were published prior to the publication of the AMSTAR checklist.

IX.II. Case-Control Summaries.

1. More than three decades ago Cramer et al. (75) evaluated 215 white women diagnosed with epithelial ovarian cancer identified through 12 hospitals in the greater Boston area. They were randomly matched by age, race and residence to 215 population-based controls. Surgical specimens were reviewed to confirm and classify tumors by histologic type. Talc exposure was determined through in person interviews. Multivariable logistic regression was used to estimate the Relative Risk. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls.

Adjusted for parity and menopausal status, this difference yielded a RR of 1.92 (95% CI: 1.27-2.89) for ovarian cancer associated with talc exposure. Women who had regularly engaged in both practices had an adjusted RR of 3.28 (95 % CI: 1.68-6.42; $P < 0.001$) compared to women with neither exposure. After adjusting for religion, marital status, educational levels, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use and smoking the RR was attenuated but remained statistically significant (RR 1.61, 95% CI: 1.04-2.49). The limitations of the study include the potential for selection bias in controls because of high rates of non-participation, although RR remained statistically significantly elevated even though the analysis was restricted to 121 cases matched with controls without a referral. Since approximately 50% of ovarian cancer cases in the Boston area was sampled, any potential for pervasive selection bias of cases was minimal. Other potential limitations include the adjustment for only a limited set of confounders such as parity and menopausal status.

2. Hartge et al. 1983 (76) conducted a hospital-based case-control study of women with pathologically confirmed primary epithelial ovarian cancers matched to equal number of women for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy in the same hospitals in Washington, DC. Controls were frequency matched for age, race and hospital. Exposure to talc was ascertained through questions about reproductive and sexual history, medical history, drug use, and other exposures. The questions for talc use were added after the study began yielding 135 cases and 171 controls.

Among the women users of talc in sanitary napkins, underwear, or the genital area there was an excess risk of ovarian cancer (unadjusted RR 2.5, 95 % CI: 0.7-10.0) which was not statistically significant due to small sample size (n= 7 cases and 3 controls). The limitations to the study include the limited number of cases and controls reporting genital use of talc (n=10) and publication as a letter to the editor which may or may not undergo peer review depending on editorial practices at the journal. They did not report adjusted results of ovarian cancer after perineal exposure to talc. Another limitation is the potential for recall bias; however, this was likely minimal given similar reporting of douching practices in cases and controls.

3. In 1988, Whittemore et al. (58) evaluated 188 pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center. The diagnoses were subsequently histologically verified. One group of controls was selected from the hospital (n=280); and a second group was selected from the population using random digit dialing (n=259). Exposure to talcum powder products was determined through a structured in-person interview at home where subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Data was recorded by type (perineum, sanitary pads, diaphragm or some combination thereof), and duration of use.

Population cases were more likely to be younger and more likely to be premenopausal than cases and hospital-based controls. Approximately 52% of cases reported talc use compared to 46% controls (RR 1.40, p=0.6). After adjusting for parity and oral contraceptive use, perineal use of talc was associated with an excess risk of ovarian cancer that was not statistically significant (RR 1.45, 95% CI: 0.812.60). Women who used talc an average of 1-20 times per month reported an excess risk in comparison to those who used it less frequently which was not statistically significant (RR 1.27, p=0.29). The risk among users of more than 20 times per month was 1.45 times greater than non-users, but the findings were not statistically significant (p=0.09). The overall increased risk in overall applications per month was 1.30 (p=0.19). Although the data showed a *trend* of increasing risk with increasing frequency of perineal exposure, the trends were not statistically significant and there was no trend with increasing duration of exposure. The risk of ovarian cancer with talc use between one and nine years was 1.6 times the risk of those with a shorter duration (95% CI: 1.00-2.57; p=0.05), and the risk among those with more than 10 years of exposure was 1.11 higher than that of non-users (95% CI: 0.74-1.65; p=0.61).

The limitations of the study are the inability to interview cases and the choice of two controls. Some amount of non-differential misclassification of exposure may bias findings towards null. The dose-response analysis was limited by the inability to determine the combined effect of frequency and duration of exposure. The study reported a statistically increased risk of ovarian cancer with coffee consumption and a non-significant reduction in risk with smoking. Subsequent meta-analysis (111) or Mendelian randomization (112) studies have confirmed that there is no association between coffee consumption and ovarian cancer, whereas smoking has a heterogenous relationship to ovarian cancer which varies by histologic subtypes. (112) The reports of such additional spurious associations suggest an element of measurement error in their database.

4. Harlow et al. 1989 (77) conducted a population-based case-control study which included 116 females 20-79 years old h *serous and mucinous borderline ovarian tumors* identified using International Classification of Disease (ICD)-9 codes from the cancer registries of three western urban counties in Washington State. An independent pathology review confirmed diagnosis for 73% of tumors with 94% agreement, so the additional 33 cases were included. A sample of 158 controls of white women was identified through random digit dialing. Women with bilateral oophorectomy were excluded from the analysis. Any exposure to talc including any perineal exposure to powder, method of use, type of powder use (cornstarch, baby powder, talc, deodorizing powder), and combinations of method and type was ascertained through in-person interviews.

The study reported no statistically significant increased risk of ovarian cancer with perineal use of dusting powders (RR 1.1, 95% CI: 0.7-2.1). When looking at unspecified talc adjusted for the same factors, the RR was 1.0 (95% CI: 0.4-2.4). However, women who reported any use of talc containing powder on sanitary napkins showed an excess risk which was not statistically significant due to limited statistical power (RR 2.2, 95% CI: 0.8-19.8). However, among the sample of women who used deodorizing powders alone or in combination with talc, the risk of ovarian cancer was RR 2.8 (95% CI: 1.1-11.7) attributed to the potential exposure to asbestos. The limitations to the study include the potential for selection bias since 30% of cases and controls did not participate, although their characteristics were like the included participants which may have limited any impact. It is also possible that these findings are limited to borderline rather than malignant ovarian cancers.

5. In 1989, Booth et al. (51) conducted a population-based case-control study of 280 cases of ovarian cancer in women under 65 years of age from 13 hospitals in London and two in

Oxford. 451 controls were selected from other hospitals as enough age-matched controls were unavailable. The study included both pre- and post-menopausal women. Ovarian cancer was determined through hospital diagnoses with pathological specimens being histologically classified. Serous tumors were most prevalent, though mucinous, endometroid and clear cell carcinoma was included. Information regarding talc exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly, or daily talc use.

After adjusting for age and social class (based on occupation of the husband for married women, and their own occupation for women who were not married) talc users reporting use more than once a week had a higher risk compared to never users. (RR 2.0, 95 % CI: 1.3-3.4). Those who reported daily use also had a non-significantly higher risk (RR 1.3, 95% CI: 0.8-1.9). There was some amount of missing data (8% of cases and 4% of controls), and no consistent trend of increasing risk with increasing frequency of use. However, data was not available on the duration of talc exposure to conduct meaningful dose-response analysis.

6. In 1992, Harlow et al. (79) included 235 cases of white women between the ages of 18 and 76 who had been diagnosed with ovarian cancer at one of 10 hospitals in the Boston metropolitan area. Controls were randomly selected from the town books; annual publication lists and address lists within 2 years of the age of case as potential controls. Cancer was confirmed through an independent pathology review. Talc exposure was determined through in-person interviews. Talc exposure from infancy with diapering, or use on other parts of the body, was not included. Talc use in other parts of body was considered unexposed. Talc use was reported as any genital application, type of application (sanitary napkin/underwear, via partner or application to diaphragm, via dusting to perineum), number of applications per month, years of use, age at first use, years since last use, whether use was before or after 1960, brand of application, estimated total lifetime applications, estimated applications excluding use after hysterectomy or tubal ligation, and estimated applications excluding use after hysterectomy or tubal ligation and use during nonovulatory months. The Chi square test for change in linear trend based on change in deviance in models.

Most participants reported use of baby powder. Perineal talc use was associated with an increased risk for ovarian cancer (OR 1.5, 95% CI: 1.0-2.1) when adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight. Perineal use of talc via dusting powder to perineum was associated with a significantly increased risk of ovarian cancer OR 1.7 (95% CI: 1.1-2.7), whereas use by sanitary napkins, underwear, use via

diaphragms was not associated with a significantly increased risk. Adjusted risk was highest for endometrioid tumors (OR 2.8, 95% CI: 1.2-6.4) and borderline tumors. A greater proportion of women with endometroid tumors reported more than 10,000 lifetime applications of talc during ovulatory cycles while having an intact genital tract compared to other histologic types (34 % vs 16%, respectively). The risk of cancer increased significantly with increased frequency of applications per month using a linear test trend as a continuous variable. The risk was highest among the women who applied talc once daily relative to non-users. Women who applied talc for more than 10 years were at 60% greater risk for ovarian cancer relative to non-users. An 80% excess risk was associated with an estimated exposure of more than 10,000 applications. The association between talc and ovarian cancer was greater than in talc products before 1960. Restricting the analysis to exposure during ovulatory months, women with intact genital tract and more than 10,000 applications during ovulatory cycles had a threefold increase in risk of ovarian cancer. Limitations included the high rates of non-response (n=31% cases and 19% of controls) and failure to adjust for family history of ovarian cancer and oral contraceptive use.

7. Chen et al. 1992 (78) evaluated 112 cases of ovarian cancer in Beijing China. The diagnosis was confirmed by laparotomy and pathological examination. Serous cancer accounted for 51% of cases, mucinous for 19%, and miscellaneous epithelial for 30% of cases. Two controls were matched for each case using random selection from the same street, office, or township. A comprehensive questionnaire was administered through face-to-face interviews and collected information about menstrual, obstetric, marital, medical, familial, and dietary histories with reference to events 3 years or more prior to diagnosis. A total of 224 controls were selected. Talc exposure was measured through a yes or no metric, for exposure occurring 3 or years prior to date of diagnosis or equivalent date in controls. Logistic regression was conducted to estimate relative risk.

The mean age of participants was 48.5 and 49 years among cases and controls respectively. After adjusting for education and parity, there was an excess risk of ovarian cancer associated with a history of long-term (>3 months) application of dusting powder to the lower abdomen and perineum (RR 3.9, 95% CI: 0.9-10.6) which was not statistically significant due to limited statistical power (n=7 cases and 5 controls reporting powder use). The limitations of the study include the small sample size, loss to follow up and death, the inability to fully ascertain all cases of ovarian cancer and the exclusion of controls with other health problems. Although the applicability of these findings from a Chinese population to a US population is limited, the

findings of an increased risk in different parts of the world provide evidence in support of an increased risk of ovarian cancer with dusting powder use.

8. In 1992 Rosenblatt et al. (80) conducted a hospital-based case-control study of the association between genital and respiratory talc exposure and the development of epithelial ovarian cancer at the Johns Hopkins Hospital. Among 140 diagnosed cases of epithelial ovarian cancer, approximately 108 were successfully interviewed. Seventy-seven pathologically-confirmed incident cases diagnosed within 6 months of admission were matched to age-race matched controls (n=46). Exposure was ascertained using a structured questionnaire administered at home and in the hospital. Conditional logistic regression was used to obtain strength of the association.

Although genital powder use was not associated with an increased risk of ovarian cancer, statistically significant increased risk was observed for exposure to talc on sanitary napkins (OR 4.79, 95% CI: 1.29-17.79) after adjusting for confounders such as obesity, socioeconomic status, religion, reproductive status and oral contraceptive use, with a smaller risk after genital bath exposure (RR 1.7, 95% CI: 0.7-3.9). An excess risk of borderline significance was seen for exposure of ≥ 37.4 years (RR 2.4, 95% CI: 1.0-5.8). The limitations include the small sample size, lack of data on frequency of talc use, and the limited generalizability of the findings from one hospital. The control group also reported a very high rate of talc use (90%) which may have limited the ability to detect any differences.

9. In 1993, Tzonou et al. (81) reported on a hospital-based study of 189 women under 75 years of age with histopathologically confirmed ovarian cancer in Athens, Greece compared with 200 hospital visitor controls in two hospitals. Control patients were those hospitalized in the same ward as cancer cases. Talc exposure was determined by asking participants to report talc use (over an extended period before the onset of illness for cases and for a comparable period among controls) among other characteristics, through interviews in the hospital. Talc use was reported as a yes/no metric. Estimates were adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status and age at menopause, parity and age at first birth, tobacco smoking, coffee drinking, consumption of alcoholic beverages, hair dyeing and mutual (analgesics-tranquilizers/hypnotics) tranquilizers.

An exceedingly small number of cases (n=6) and controls (n=7) reported perineal use of a talc. There was no statistically significant increased risk of ovarian cancer associated with perineal application of talc (RR 1.05; 95% CI: 0.28 to 3.98). The limitations of the study include the low

proportion of talc exposure, which was ascertained in only approximately 3% of cases and controls.

10. In 1995, Purdie et al. (82) evaluated 824 histologically confirmed cases of epithelial ovarian cancer and 860 controls from gynecological oncology treatment centers in the three most populous Australian states. Controls were selected from electoral rolls in Australia where electoral participation is mandatory using a random procedure to match the age distribution of cases. Talc exposure was determined through face-to-face interviews conducted by trained interviewers using a standard questionnaire.

After adjusting for parity, there was a statistically significant increase risk of ovarian cancer reported with talc use on the abdomen or perineum (OR 1.27, 95% CI: 1.04-1.54). The limitations include high non-response rates in controls which may differ from the source population, but the age distribution of controls was like non-responders suggesting minimal response bias by age. There is also the possibility of bias in the selection of cases. They only adjusted for a limited set of confounders. Some misclassification of outcome is also possible given borderline and malignant cases were lumped together, although no differences were found when results were analyzed separately. Recall and interviewer bias was minimized by trained interviewers who administered standardized questionnaires.

11. In 1996 Shushan et al. (83) reported on findings from a study of two hundred living cases aged 36-64 years with history confirmed diagnosis of primary invasive or borderline invasive ovarian cancer in the Israel Cancer registry. There were 408 women from the same area selected by random digit dialing. Both were interviewed using standardized questionnaires.

A larger proportion of cases than controls reported using moderate to a large amount of talc (10.5% vs 5.6%; P=0.04) compared to never users or seldom users, a difference which was statistically significant. Limitations include high refusal rate for cases (30%), the low rates of talc exposure among controls and limited adjustment for confounders. (14)

12. In 1997, Cook et al. (84) reported on 329 white women between the ages of 20-79 diagnosed with epithelial and borderline ovarian cancer identified through the Cancer Surveillance System of Western Washington. Women were randomly selected as controls using random digit dialing from a larger pool of women for cancer studies. Genital powder exposure was collected through structured in person interviews and reported as any lifetime powder application, method of use (perineal dusting only, diaphragm only, sanitary napkin only, or genital deodorant spray only). Additional exposure information included cumulative

lifetime days of use for dusting and similar metrics for other methods of use. Genital powder use was also separated into use of talcum powder, baby powder, cornstarch, deodorizing powder, bath/body powder, or unspecified powder. Analysis was presented by age because adjustment for other confounders such as income, marital status, body mass index, oral contraceptive or parity did not change results.

Genital powder exposure was more common among cases (50.8%) than controls (39.3%). After adjusting for age, any use of genital powder was associated with a statistically significant increased of ovarian cancer (RR 1.5, 95% CI: 1.1-2.0) compared to non-use, although there was no clear pattern of increasing risk after increasing duration of use. After adjusting for age, exclusive use of perineal dusting was also associated with a statistically significant increased risk of ovarian cancer (RR 1.8, 95% CI: 1.2-2.9), whereas the risks for use via other routes of exposure (e.g. diaphragms, powder) were not significant. There was a statistically significant increased risk of serous tumors associated with any genital powder application (RR 1.7, 95% CI: 1.1-2.5), but not for the smaller number of mucinous or endometroid tumors. Limitations include low participation rates (64.3% for cases, 68% for controls), the potential for recall bias, and confounding by family history of ovarian cancer in a study where more than 50% of controls were less than 45 years of age.

13. In 1997, Chang et al. (56) conducted a population-based case study of cases of borderline and invasive histologically confirmed ovarian cancer among participants aged 35 to 79 years from Canada. Talc exposure was determined through a questionnaire conducted during an in-home in person interview to detail medical and reproductive histories. Powder use was reported as talc, cornstarch, or a mixture. Information was provided for type of exposure, number of uses per month, years of use, years of use pre- and post-1970, and well as years of use before and after a tubal ligation or hysterectomy. They adjusted for age, years of oral contraceptive use, number of full-term pregnancies, duration of breastfeeding per pregnancy, tubal ligation, hysterectomy, and having a mother or sister with breast or ovarian cancer.

Talc exposure was reported in 44% of cases and 35.6% of controls. After adjusting for confounders there was a statistically significantly increased risk of ovarian cancer associated any talc exposure via sanitary napkins, direct application to the perineum or both (OR 1.42, 95% CI: 1.08-1.86). The dose-response analysis showed a borderline-significant association was detected between duration of after-bath talc exposure and risk (OR 1.09, 95% CI: 0.98-1.21, per 10 years of exposure), without any significant association between frequency of exposure and

risk. Although risk was elevated for both invasive and borderline carcinomas, it was statistically significant only for invasive carcinoma. The limitations of the study include the potential for recall bias and the high rates of non-response (28.7% for cases and 35.5% for controls)

14. Green et al. 1997 (62) conducted a population based case-control study of 824 women aged 18-79 with histologically confirmed ovarian cancer compared to 824 controls. The methods and limitations were similar to the study by Purdie et al. (82). The prevalence of talc use was approximately 40% in the control use. Perineal talc was significantly associated with ovarian cancer (RR 1.3, 95% CI: 1.1-1.6), without any effect of longer duration of talc use. Compared to women who had neither used talc nor had sterilization, the risk was highest among talc users without surgery like the findings by Whittemore et al. (58). There is the potential for recall bias, and the quantity of talc use was unknown.

15. In 1998, Godard et al. (85) examined 170 French-Canadian women with a histologic diagnosis of ovarian cancer from 2 large Montreal teaching hospitals. Cancer diagnoses were histologically confirmed, and pathology reports were reviewed for tumor classification. 170 population-based controls were identified using modified random digit dialing to match the age distribution of cases. Talc exposure was obtained through a 57-item questionnaire. 70% of interviews were conducted in person in clinics and 30% were conducted via phone. Talc use was reported through an ever/never metric for perineal use.

Only 10.6% of cases and 4.7% of controls reported talc use. As a result, perineal talc use was associated with an increased risk for ovarian cancer which was not statistically significant (RR 2.49, 95% CI: 0.94-6.58; P = .066) because of limited statistical power. Similar patterns of excess risk which did not reach statistical significance were seen in both the comparisons for sporadic and familial cases and controls. The limitations of the study include a modest non-response rates among cases (13%) and controls (10.7%).

16. In 1999, Cramer et al. (57) evaluated 563 ovarian cases identified through tumor boards and statewide cancer registries in Massachusetts or New Hampshire in a population-based control study. Pathology reports were reviewed, and slides were sought in any case where there was a discrepancy between histologic description and final diagnosis. Controls were selected from the population using random digit dialing with a response rate of 72% among eligible controls. Talc exposure was obtained through questionnaires in which potential controls and cases were blinded. Specific hypothesis regarding talc use were not discussed. Exposure was assessed prior to 1 year before date of diagnosis or date of interview for

controls. Talc use in the genital or rectal area, on sanitary napkins and on underwear was considered as exposure whereas non-use and non-genital use was considered as unexposed. Exposure from condoms and diaphragms was not assessed.

Genital talc exposure was reported in 27% of cases and 18.2% of controls and the average duration of talc use exceeded more than 20 years in cases and controls. There was a statistically significantly increased relative risk of ovarian cancer with genital talc exposure 1.60 (95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, or primary relative with breast or ovarian cancer. The highest risk was seen among women whose age at first use was between 20 and 25 (RR 1.87, 95% CI: 1.03-3.39) those who have used talc for less than 20 years (RR 1.86, 95% CI: 1.16-3.00), those whose total applications is less than 3000 (1.84, 95% CI: 1.12-3.03), women who used talc when nulliparous (RR 2.80, 95% CI: 0.64-12.20), and those with serous invasive tumors (RR 1.70, 95% CI: 1.22-2.39). Only one case and 3 controls reported primarily using cornstarch, these numbers are likely accurate for talc use, despite the potential for including other kinds of powders. There was little evidence of effect by confounders such as age, oral contraceptive use and parity. Linear trends were significant in models that included women who were not exposed without any clear trend in duration or intensity of exposure in models that excluded women who were not exposed. Analysis of dose-response censured after closure of female tract or non-ovulatory cycles, and models showed a trend this was statistically significant only after inclusion of non-genitally exposed categories (P_{trend}=0.022).

Potential limitations include the potential for recall bias, although this is likely to be minimal and more likely to occur for short term exposures rather than long term exposures. The evidence for substantial degree of recall bias is refuted by the findings that there is no evidence of higher proportion of perineal talc exposure reported among cases in more recent compared to older studies to suggest stimulated reporting, no evidence of significant excess of non-genital talc exposure among cases, and the excess is limited to invasive serous carcinoma,(84) rather than all types of ovarian cancer or endometrial carcinoma.

17. In 1999, Wong et al. (86) reported-on a hospital-based study of 499 patients with epithelial ovarian cancer and 775 age-matched controls with non-gynecologic cancer diagnoses. Cancer diagnoses were confirmed in the cancer registry. Exposure was ascertained through self-administered questionnaire in which approximately 15% of participants did not respond to questions about talc use or its frequency.

Talc use was reported by 47.8% of cases and 44.9% of controls. Genital talc use was reported by 34% of cases and 32.2% of cases. The mean duration of talc use was 22 years in controls and 21 years in the study population. After adjusting for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy there was no statistically significant increased risk of ovarian cancer among ever users of talc (OR 0.92, 95% CI: 0.24-3.62). There was no significant association between duration of use and development of ovarian cancer even after prolonged exposure of more than 20 years. However, when evaluating genital talc use via histologic subtypes of cancer, all ORs were above 1 (except for undifferentiated carcinoma) but were not statistically significant. Similarly, those who had no history of genital tract interruption the ORs were elevated but not statistically significant. However, the study was limited by the non-response rate and the choice of a controls with malignancies. (113). Additionally, data on exposure were reported on a self-administered questionnaire rather than administered by interviewers. The results could not rule out the effect of talc exposure via condom use and data was not available on the frequency of talc use.

18. Ness et al. (87) conducted a population-based control study. Cases (20-69) years of age with recent diagnosis of ovarian cancer (n=) were compared with community-based controls 65 years or younger through random digit dialing. Controls were age-matched as well as matched by last 3 digits of the phone number. Approximately 72% of controls were selected. As a part of detailed interviews with calendars women were asked about their reproductive history including talc use. The question was, "As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least once per month for 6 or more months on your: 1) feet, arms, or breasts, but not the genital or rectal areas? 2) genital or rectal area? 3) on your sanitary napkins? 4) on your underwear? 5) on your diaphragm or cervical cap?" They were then asked whether they had a male sexual partner(s) for more than a year who regularly used such products on his genital area or underwear. The duration of use of talc for each of these modes of use was also queried. The estimates were analyzed using conditional logistic regression after adjusting for age and gravidity (each as continuous variables), race (white/black/other), history of ovarian cancer in any first degree relative (yes/no), oral contraceptive use (yes/no), tubal ligation (yes/no), hysterectomy (yes/no), and breast-feeding (yes/no).

Talc use was reported in 53.2 % of controls. Compared to never talc use, talc use on all parts of the body (OR 1.4, 95% CI 1.1-1.6), genital/rectal (OR 1.5, 95% CI 1.1-2.0) on sanitary napkins

OR 1.6, 95% CI 0 1.1- 2.3) and underwear OR 1.7, 95% CI. 1.2-2.4) was associated with a statistically significantly increased risk of ovarian cancer after adjusting for confounders. However, talc use on diaphragms (OR 0.6, 95% CI 0.3-1.2) or by male partner (OR 1.0, 95% CI 0.7 to 1.4) was associated with an increased risk which was not statistically significant. Although duration of talc use did not show a pattern of increased risk with increased risk with duration of exposure, the OR for each categories (> 1 year, 1-4 years, 5- 9 years and > 10 years) were elevated and were statistically significant for 1-4 years. Tubal ligation and hysterectomy decreased ovarian cancer risk. Limitations to the study include the low response rates among cases and controls due to exclusion of prevalent ovarian cancer. Recall bias while always a concern was less likely to be a concern given that risk factors overall did not increase risk but were limited to those linked to inflammation.

19. In 2004, Mills et al. (59) conducted a population-based case-control study of 256 women with histologically confirmed incident epithelial ovarian cancer from 22 counties in Central California. They also selected 1122 controls who were residents of that area who had one intact ovary and no history of ovarian cancer. Talc exposure was determined through phone interviews conducted by trained interviewers. Talcum powder use in the genial area was reported as an ever/never metric, as well as by frequency, duration, and cumulative use. The final parsimonious model adjusted for age, race, duration of oral contraceptive use and breast feeding.

The rates of talc use in controls was 37.1 % and higher among white non-Hispanics. Controls were more likely to have been outside the US. Most of talc exposed cases and controls were non-white. There was a statistically significant risk of ovarian cancer associated with genital talcum powder use (OR 1.37, 95% CI: 1.02-1.85) after adjusting or age, race, duration of oral contraceptive use, and breast feeding. Although increasing frequency of use showed a 74% increased risk among women who used talcum powder more than 4-7 times per week (P_{trend}= 0.015), this risk was not monotonic because risk the decreased between second (rarely to several times per month) and third categories (1 to 3 times per week). Duration of use also showed increasing risk and peaking between 4-12 years of use and declining thereafter (P_{trend} =0.045). Cumulative exposure increased in the second and third quartiles of exposure but declined among the highest quartile of users (P_{trend}=0.051). The risk was highest among those who had stopped using talcum powder in the last 1-2 years compared to those in the more distant past. The risks were primarily elevated for serous and mucinous tumors. Risk was higher among those reporting use after 1975 which may be related to the recency of use, and those after age 20. Limitations of the study include a low response fraction which was only

40% for eligible cases and 57% for eligible cases, and high rates of non-participation- 34.2% among cases and 29.3% among controls. The dose-response analysis did not exclude exposure during non-ovulatory periods or after gynecologic surgery which may have diluted the relative risk estimates. However, strengths include the ability to rule out prevalent cases by examining incident cases alone.

20. In 2004, Langseth et al. (88) conducted a case-control study of pulp and paper workers from different mills in Norway. Only one of these mills reported use of fibrous talc. They included 46 cases and reviewed histological records for each case. Most of the cases were invasive tumors. Four controls free of ovarian cancer and having intact ovaries were matched by birth year +/- 2 years and were drawn by incidence density sampling. A total 179 controls were available for analysis. Talc exposure was determined through personal interviews which took place in mill offices, at home, at a medical institution, or by phone. Talc exposure was reported environmentally and as use by personal hygiene (diapers, sanitary napkins, non-genital area or husbands use in genital area)

Talc exposure was reported among 50% of cases and 48% of controls. After adjusting for number of children, breastfeeding, age at birth of first and last child, age at menarche, age at menopause, smoking, and family history the use of talc use by personal hygiene was associated with an excess risk of ovarian cancer OR 1.15 (95% CI: 0.41-3.21), which was not statistically significant. The study has significant limitations. The sample size of the study was low with limited statistical power to detect a two-fold increased risk with a probability of only 53 % and response rate for interviews were low -76.1% for cases and 65.7% for controls. The inclusions of non-genital or husband's use in genital area among the exposed category diluted the estimates of relative risk for ovarian cancer associated with talc exposure. More information on cases was collected from relatives than controls because 71.5 of cases were deceased compared to only 28.6% of controls. The rates of missing data on talc use was high, because it was obtained from proxy respondents introducing an element of uncertainty in the estimates for relative risk of ovarian cancer associated with talc use.

21. In 2008, Merritt et al. (89) reported on a population-based study of 1,576 women with epithelial ovarian cancer as part of the Australian Ovarian Cancer Study. Pathology reports and diagnostic slides were reviewed for a sample of 87 women with 97% agreement with original abstracted data. Cases were confirmed by histopathology. 1509 controls were selected from the electoral rolls and were matched by age and residence. Talc exposure was identified through a comprehensive health and lifestyle questionnaire. Talc use was reported as

ever/never for perineal use (powder or talc in the genital area or on underwear or on sanitary napkins), years of use prior to surgery, use post-surgery, and use stratified by age at diagnosis. All analyses were conducted for talc use while the reproductive tract was patent and exposure occurring 12 months prior to the diagnosis of cases and similar period in controls was excluded.

The rate of talc use was 43% among controls and 46% among cases. When adjusted for age, education, parity, and oral contraceptive use of talc in the perineal region among women with patent tubes there was a statistically increased risk of ovarian cancer (OR 1.17, 95% CI: 1.01-1.36) with the highest risk reported for serous tumors (OR 1.21, 95% CI: 1.03-1.44). The tests for trends for duration of use were of borderline statistical significance for all cancers and serous subgroup (P_{trend} =0.02 for both). No significant associations between number of years used pre- or post-surgery and significantly elevated risks for overall cancer and serous ovarian cancer were seen in women both above 70 years of age, and below 50 years of age suggesting that timing of talc exposure (before or after 1976) did not affect results. There was no association between PID and the risk of ovarian cancer or the protective effect of NSAIDs. Limitations include low response rates and the lack of data on the frequency of exposure.

22. In 2008 Gates et al. (55) conducted a nested case-control study as part of the New England Case-Control study and the Nurses' Health Study (NHS). Further cohort analysis from the NHS are presented in the section on cohort studies below. **Section IX.III.I** Ovarian cancer diagnoses were confirmed by the researchers. They included 1385 cases and 1802 controls. 76.7 % of cases were incident with respect to the timing of DNA collection in the NHS. Exposure was accessed through a questionnaire that asked questions related to use of talcum powder. The NECC questionnaires included questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or non-genital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week, or daily) or to sanitary napkins (yes/no). The study defined regular genital talc use as application of powder to the genital/perineal region at least once per week. We also created a categorical variable for frequency of talc use, using the categories from the NHS questionnaire.

Most of the participants were white. Regular genital talc was reported among 56 cases and 44 controls, and daily genital talc use reported among 35 cases and 25 controls, respectively. There was a statistically significant increased risk of total epithelial ovarian cancer (RR 1.36, 95% CI: 1.14-1.63; P<0.001) and of serous invasive subtype (RR 1.60, 95% CI: 1.26-2.02) associated with regular use of talc when adjusted for age, study center, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of hormone use. The New England Case-control study had a higher RR associated with genital talc use than the Nurses' Health which had a smaller sample size. There was a statistically significant trend between increasing frequency of talc use and risk of both total and serous invasive ovarian cancer in the pooled analyses (P *trend* < 0.001 for both total and serous invasive ovarian cancer). The association between talc and ovarian cancer was stronger among women with the glutathione S-transferase M1 (GSTM1) null genotype (P interaction = 0.03), particularly in combination with the GSTM1 present genotype alone (P interaction = 0.03) in two independent study populations. The strengths of the study include robust findings from two independent study populations. Although talc exposure was only measured in the 1982 NHS questionnaire when participants were between 36 to 61 years of age, the number of users who began talc use after this is likely small as shown by the fact that more than 95% of controls with regular talc in the NECC reported talc use before age 35. The consistent findings from the prospective NHS study and the NECC may have minimized any potential biases due to the case-control design. Since talc exposure was defined as at least once per week, such habitual exposure is less susceptible to recall bias than sporadic exposure.

23. In 2009, Wu et al. (48) conducted a population-based study of 609 cases of women and 688 controls between the ages of 18 and 74 residing in Los Angeles with histologically confirmed incident invasive or borderline ovarian cancers. Cases were identified through the Surveillance, Epidemiology and End Results (SEER) Program. Cases were matched to neighborhood controls on age and race/ethnicity. Controls were women with one intact ovary with no history of cancer except non-melanomatous skin cancer matched on age and race/ethnicity. Talc exposure was determined through a detailed interview by the same person which included a comprehensive questionnaire that used a reference date of 2 years before the date of diagnosis (or date of interview for controls). Talc use was reported as a yes or no metric (including yes or no for perineal area use), frequency and duration, total times of use, and total times of use before and after 1975. Few users of talc (24) had tubal ligation or hysterectomy prior to talc use and were considered as non-users.

The cases were primarily white woman but also included 41 African American women, 136 Hispanic women, and 51 Asian women. After adjusting for race, age, education, tubal ligation, family history, menopausal status, use of oral contraceptives, and parity perineal use of talc was associated with a statistically significantly increased risk of ovarian cancer (RR 1.53, 95% CI: 1.13-2.09). Elevated risks were also noted among those who used it on sanitary napkins, underwear and on diaphragms but not significant due to limited statistical power. There was a clear trend of increasing risk with increasing frequency of use among users who had used it for more than 20 years. The risk of ovarian cancer increased significantly with increasing frequency and duration of talc use; compared to never users, risk was highest among long duration (20 years), frequent (at least daily) talc users (RR 2.08, 95% CI: 1.34-3.23). The risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975 (P_{trend} <0.001). The association between talc use and ovarian cancer was strongest for serous ovarian cancer. Risk of ovarian cancer increased with the diagnosis of endometriosis. Limitations include the rates of non-response among cases and controls, and classification of talc use among a small number of users with prior hysterectomy as being non-exposed. However, the effect of this misclassification is likely to be minimal.

24. In 2009, Moorman et al. (90) reported on a study involving 1,114 cases with histopathologically confirmed tumors as part of the North Carolina Ovarian Cancer Study. newly diagnosed cases were identified through the North Carolina Central Cancer Registry. All cases were confirmed by histopathologic review. Controls were frequency matched to cases and recruited from the same geographic region using random digit dialing. The controls could not have had a bilateral oophorectomy. Talc exposure was reported through in-person interviews conducted by nurses with life calendar and pictures of contraceptives, menopausal hormones, and other medications were used to help aid recall. Talc use was reported as a yes/no metric.

The analysis focused on invasive ovarian cancer which comprised of 78% of cancers for African-Americans and 79% for whites. Among controls, talc use was reported by 23.9% among whites and 31.2% of African-Americans. After adjusting for age there was an excess risk reported for both whites (OR 1.04, 95% CI: 0.82-1.33) and African Americans (RR 1.19, 95 % CI: 0.68-2.09) which were not statistically significant. Limitations include the high rates of non-response (33.5% among cases, 39.1% among controls), with higher non-response rates among African-Americans. There was a large proportion of missing data on talc use for cases and controls; 23.6% and 38.5% among whites, respectively, and 25.2% and 29.1% among African Americans, respectively, resulting in misclassification of exposure. The authors did not

clarify the route of talc exposure and may have classified non-genital talc exposure to the talc exposed group which may have diluted the RR. Additionally, the study did not adjust for confounders to address the timing, frequency and duration of talc exposure, or whether talc exposure occurred before or after tubal ligation or hysterectomy.

25. In 2011, Rosenblatt et al. (60) reported on a study of women between the ages of 35 and 74 from 13 counties in Washington state. Cases of borderline or invasive epithelial ovarian cancer were identified through the Cancer Surveillance System. Controls were selected from the population using digit dialing. Talc exposure was determined through in person interviews which included a reference period of unstated length before diagnosis or interview. For powder use on sanitary napkins and deodorant spray, the total number of months of use was recorded. For powder use on perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Talc use was reported as genital powder exposure by type of use, duration of use, lifetime applications, age at first use, age at last use, calendar year of first use, time since first use, and time since last use.

Perineal use of powder after bathing was reported in 12% of controls. Reporting of cornstarch was uncommon in the study. After adjusting for age, calendar year of diagnosis, county of residence, number of full term live births, and duration of hormonal contraception the perineal use of powder after bathing was associated with an increased ovarian cancer risk (OR 1.27, 95% CI: 0.97-1.66) which was not statistically significant, but a statistically significant increased risk was seen among women with borderline tumors (OR 1.55, 95% CI: 1.02-2.37), similar to that reported by Harlow et al. (79) There were no differences in risk among various types of powder use, as the risk among those who reported use of talcum powder was RR 1.38 (95% CI: 0.77-2.47). There was no difference in exposure outcome relationship between talc use before and after 1980. There was no pattern of risk associated with perineal dusting powder and the increasing extant of use as defined by years in which it was used or number of lifetime applications. The participation rate of cases and controls was modest at 76.8% and 69%. Some misclassification of exposure is possible as participants may be unable to provide accurate information on whether the specific powder contained talc. However, the presence of talc, rather than a specific dose, is the primary determinant of exposure in which case genital powder use is a reasonable proxy for talc exposure.

26. Kurta et al. 2012 (91) reported on a case-control study from the Hormones and Ovarian Cancer Project using 902 ovarian cancer cases and 1802 controls. Participants were diagnosed with histologically confirmed ovarian, fallopian tube or peritoneal cancers. They were at least

9 years old and within 9 months of diagnosis. Controls were frequency matched by age and area code to cases at 2:1 ratio. Trained interviewers collected data via questionnaires. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins or underwear or on diaphragms or cervical caps.

Perineal talc use was reported among 20.9% of controls and 27.6% of cases. After adjusting for age, race, education perineal talc was associated with a statistically significantly increased risk of ovarian cancer OR 1.40 (95% CI: 1.16-1.69). Limitations include the population which was women seeking treatment for infertility which may limit generalizability.

27. In 2015, Wu et al. (53) evaluated 1,701 newly diagnosed histologically confirmed cases of invasive epithelial ovarian cancer cases of ovarian cancer among participants aged 18 and 74 in Los Angeles county identified through the USC Cancer Surveillance Program. Cases were primarily white but 308 Hispanic Women and 128 African American women were also included. Controls were selected from residents of LA county and were matched to cases on race/ethnicity and year of birth. Talc exposure was ascertained through in person interviews conducted using standardized questionnaires with a reference date of 12 months prior to diagnosis (or date of interview for controls). Genital talc was reported as no use or less than one year of use, yes use, and use per 5 years of talc.

Among controls the prevalence of talc use ≥ 1 year was 30.4% in non-Hispanic whites, 28.9% in Hispanics and 44.1%. After adjusting for several confounders including race, age group, menopausal status, age at menarche, hormone therapy use, BMI, income, education, life births, tubal ligation, oral contraception, endometriosis, and first-degree family history of ovarian cancer there was a statistically significant increased risk of ovarian cancer associated with genital talc use across all races (OR 1.46, 95% CI: 1.27-1.69), non-Hispanic whites (OR 1.41, 95% CI: 1.21-1.67), and Hispanics (OR 1.77, 95% CI: 1.20-2.62) compared to non-use or less than 1 year of use. The risk was elevated but not statistically significant among African-Americans (OR 1.56, 95% CI: 0.80-3.04) because of low statistical power for the subgroup. Every 5-year use of talc was associated with a statistically significant risk of cancer among the overall population (OR 1.14, 95% CI: 1.09-1.20) and non-Hispanic whites and Hispanics, whereas the excess risk among African-Americans was not statistically significant. The non-response rate for cases (36.8%) and controls was modest. There was no evidence of systematic bias in the ascertainment of exposure as prevalence of various conditions such as endometriosis was consistent with other prior studies.

28. Schildkraut et al. 2016 (52) evaluated African women aged 20-79 years of as part of the African-American Cancer Epidemiology Study. They selected 584 cases of newly diagnosed epithelial ovarian cancer and matched 745 controls to cases on age and region of residence using random digit dialing. Talc exposure was determined through a telephonic interview which included information on baby powder use. Participants were considered regular users if they reported use at least more than 1 time per month for 6 months. Regular users were asked about genital or nongenital use, frequency, duration, and lifetime applications (number of applications per month by number of months used). Since there was a small number of users who reported only genital powder use, they were grouped with genital and non-genital users to "any" genital use. Exposure was examined by frequency of use (less than 30 times per month, daily), duration of use (<20 years, ≥20 years) and lifetime number of applications (<3600, ≥3600). They also assessed for reporting biases and the effect of stimulant reporting because of the filing of class action lawsuits.

The median duration of body powder use in both cases and controls was 20 years and body powder use were reported among 52.9% of controls. After adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first degree family history of breast or ovarian cancer, and interview year there was a statistically significant increased risk of ovarian cancer with any genital powder use (OR 1.44, 95% CI: 1.11 to 1.86). There was a stronger association for ≥20 years of any genital powder exposure compared with <20 years of exposure and the test for trend was significant (P_{trend} =0.002). Similarly, the ORs for association between daily any genital powder users and EOC were larger in magnitude than never users, and the test for trend was significant (P_{trend} <0.01) There was also evidence of dose-response for any genital powder for the cumulative number of life-time applications with a higher risk among those with lifetime applications ≥3600; the test for trend was significant (P_{trend} <0.01). A stronger association was reported among post-menopausal women who used HRT compared to non-users. There was also an increase associated with non-genital powder exposure (OR 1.31, 95% CI: 0.95-1.79) which was not statistically significant. There was no evidence of statistically significant increased risk with "only" non-genital users and serous ovarian cancer but was statistically significant increased for non-serous ovarian cancer.

Limitations include the assessment of data by self-report. The underreporting of powder use in the abdomen which may reach the genital area may have resulted in a spuriously increased risk among "only" non-genital users or such an effect may be specific to African-American users. Although there was some evidence that there was more reporting of genital powder use

after class action lawsuits in 2014, recall bias alone is insufficient to explain these findings because there was a statistically significantly increased risk both before and after 2014.

29. In 2016, Cramer et al. (54) included 2,041 ovarian cancer cases from Eastern Massachusetts and New Hampshire as part of the Nurses' Health Study and the Ovarian Cancer Association Consortium. Pathology reports were reviewed to confirm diagnosis. The population was primarily white with less than 30 participants who were African Americans, Hispanics, Asians, or other race/ethnicities. Controls were identified through random digit dialing, driver license and town-resident lists and were frequency matched to cases by age and residence. Talc exposure was determined through in person interviews with a reference point 1 year prior to diagnosis or date of interview (for controls). Subjects were asked whether they regularly or monthly applied powder to the genital or rectal area, or on sanitary napkins, tampons or on other non-genital areas. Talc exposure was reported as personal use, potential exposure with no personal use (diaphragm, condoms, partner use), any genital powder use, type of genital powder use (cornstarch, baby powder, other), age of first use, time since exposure ended, frequency of use, years used, months per year of use, and total applications. Lifetime application was assessed by multiplying frequency of application per month with months of exposure. This was divided by 360 to yield talc years which were partitioned into separate quartiles for dose-response analysis. The study adjusted for a variety of confounders, with adjustments for age, study center, study phase, race, BMI, height, weight, parity, breastfeeding, oral contraceptive use, IUD use, ovulatory cycles, endometriosis or painful periods, Jewish ethnicity, family history, personal history of breast cancer, menopausal status, current smoking, ever smoked, asthma, alcohol consumption, and acetaminophen, aspirin or ibuprofen use.

Any genital powder use was reported in 26% of controls. The women who exclusively used cornstarch were considered unexposed. Most talc users began talc exposure around the age of 20. Overall, genital powder use was associated with a statistically significant increased risk of ovarian cancer (OR 1.33, 95% CI: 1.16-1.52) adjusted for age, study center and phase. BMI, smoking and alcohol use did not alter the association by more than 10% suggesting a lack of confounding. Most women reported using Johnson's Baby Powder and Shower to Shower with a trend for increasing risk by talc years. The trend for frequency of use was significant, but the trend for duration of use was flat. The talc ovarian cancer association was largely confined to premenopausal women and post-menopausal women with hormonal therapy. Sensitivity analysis indicated that the risk of misclassification of exposure in controls would have to very high (18%) to nullify the increased risk shown in the study. No data is available

on the extent of misclassification of talc exposure. Although some amount of misclassification is possible in retrospective studies, such a large amount is unlikely as shown by estimates from other analogous exposure-outcome association such as alcohol and breast cancer in the Nurses' Health Study. (114).

IX.III Cohort Studies. I will discuss the cohort studies below. However, it is important to emphasize that none of the cohort studies discussed below were designed to evaluate the association between talc use and ovarian cancer at the time of cohort assembly. In other words, evaluating the association between talc use and ovarian cancer was not the a-priori primary objective of the study but evaluated as a subsequent hypothesis, with its inherent limitations. For example, the NHS cohort was assembled in 1976 but data on talc use was not collected until 1982. (14). In contrast the primary objective of most case-control studies noted above was to evaluate the risk of ovarian cancer associated with talc use.

IX.III.I. In 2000, Gertig et al. (14) reported on an analysis from the U.S. Nurses' Health Study. 121,700 registered nurses were enrolled in the study; 78,630 were included in the cohort study; and 307 cases of ovarian cancer in 11 states. Notably, the Nurses' Health Study was a broad-based study of women's health. Ovarian cancer information was obtained through a questionnaire mailed to married female nurses 30-55 years which were updated every 2 years. Talc exposure was obtained from a survey question which asked "Have you ever commonly used talcum, baby powder, or deodorizing powder a) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or b) to apply on sanitary napkins? No, Yes." Frequency was thus both reported as an "ever, never" metric as well as applications per week but duration of use was not recorded. Information gathered by a questionnaire requesting information on perineal talc use was ascertained only in 1982, and never updated during follow-up. Medical records were obtained for women reporting diagnoses of ovarian cancer or those participants who died (mortality follow up was 98% complete). Histologic subtypes of ovarian cancer were determined from pathology reports and classified as serous (cystadenocarcinoma and papillary adenocarcinoma), mucinous (mucinous papillary adenocarcinoma and adenocarcinoma), endometrioid (clear cell and mixed epithelial), and borderline. Cases of epithelial ovarian cancer (ICD 183.0) confirmed by medical record review or death certificate between 1982-1996 were included in the analyses. Participants who did not respond to the 1982 question on talc use were excluded, as were participants with cancer other than non-melanomatous skin cancer, bilateral oophorectomy, ovarian removal and those with radiation therapy. They included 307 cases of ovarian cancer among 984,212 person-years of follow up (0.03% PYs or 31.2/100,000 PYs). Information on covariates was obtained from the

biennial questionnaire and included oral contraceptive use, tubal ligation, parity, family history (not asked until 1992), smoking and BMI. Age adjusted incidence rates were calculated after adjusting for covariates above, as well as age at menarche, duration of breast feeding, age at menopause. 40.4% (n=31789) reported ever talc use of which 14.5% were ever daily talc users. Women who were talc users and did not have a tubal ligation had no increased risk of epithelial ovarian cancer with talc use- no evidence of interaction. There was an increased risk for histologic subtypes of ovarian cancer with talc use which was not statistically significant (RR 1.09, 95 % CI: 0.86-1.37) after adjusting for age, duration of oral contraceptive use, body mass index, tubal libation history, smoking status, and postmenopausal hormone use. While daily talc use on perineum (RR 1.12, 95% CI: 0.82-1.55) or use less than once/week (RR 1.14, 95% CI: 0.81-1.59) was associated with an excess risk which was not statistically significant, the point estimates for talc use on perineum 1-6 times/week (RR 0.99, 95% CI: 0.67-1.46) and on sanitary napkins (yes/no) (RR 0.89, 95% CI: 0.61-1.28) were lower than 1, and these confidence intervals may not rule out an increased risk. Importantly, there was a statistically significant increased risk for ever talc use for serous invasive cancers (RR 1.40; 95% CI: 1.02–1.91). For women who reported ever daily use, the RR for serous invasive cancer was 1.49 (95% CI: 0.98-2.26). The RRs for ever-users of less than 1 time/week and of 1-6 times/week were 1.29 (95% CI: 0.81-2.04) and 1.49 (95% CI: 0.77-2.11), respectively (P_{trend}=0.05). Women above age 45 in 1982 who reported ever talc use had a higher risk of serous invasive cancer (RR 1.51, 95% CI: 1.07-2.15).

The strengths of the study include the prospective design which reduces the risk of recall bias. The relatively short follow up period may have been unable to determine ovarian cancer. The NHS cohort was not primarily designed to evaluate the association between talc and ovarian cancer. Further, as discussed above, determining "never" use based only on a one-time question near the start of the study (14 years prior to terminating the study in 1996) introduces unidirectional "behavioral change" bias, likely misclassifying some "ever" users who used talc during the study as "never" users; and biased the findings towards the null. The exclusion of prevalent cases of ovarian cancer allows one to determine the influence of exposure on incident ovarian cancer, it also introduces an element of selection bias. Of the initial cohort of 121,700 volunteers, only 78,630 women were enrolled. It is not known whether any (or how many) of the 43,000 excluded women had ovarian cancer, nor whether any (or how many) of any such ovarian cancer volunteers excluded were talc users. They could not determine the intensity of exposure as they had no information on duration of talc exposure, or number of life-time applications or the age at which talc was initiated. The study was not a "new user design" and

used prevalent rather than incident users, and is susceptible to "prevalent user biases." (15) Prevalent users are "survivors" of the early period of talc use, which can introduce substantial bias if risk varies with time. This may bias findings towards the null due to the "depletion of susceptibles." They had no data on the intensity of exposure because there was no data on the duration of talc use, or number of life-time applications. The analysis on tubal litigation could not determine whether talc use was initiated after tubal ligation. Any such misclassification of exposure is also likely to be non-differential and bias towards the null.

As a continuation of the Nurses' Health Study, in 2010, Gates et al. reported on 924 cases of the ovarian cancer as part of Nurses' Health Study with ovarian cancer confirmed by a gynecologic pathologist review of medical records. (92). They evaluated the findings between risk factors for ovarian cancer and histologic subtypes of ovarian cancer and information on talc exposure was collected through biennial questionnaires. Talc use was reported as either greater than or less than once a week. After adjusting for body mass index activity, past smoking, current smoking, family history of breast or ovarian cancer, age, parity, parous status, breastfeeding, oral contraceptive use, tubal ligation, hysterectomy, age at natural menopause, and estrogen use they reported a non-significantly increased risk of all epithelial ovarian cancer (RR 1.06, 95% CI: 0.89 to 1.28) with genital talc use > once/week compared to < once a week. Although the estimates for the RR were higher for mucinous subtype (RR 1.50, 95% CI 0.84-2.66), there was no evidence of interaction across the subtypes ($P_{heterogeneity}$ =0.55) in this analysis. The strengths and weaknesses of this study are largely like the Gertig analysis of the NHS cohort above, with the additional limitations in the low number of cases (only 29 cases of epithelial ovarian cancer among genital talc users in 108, 870 women).

IX.III.II. In Houghton et al. (17) reported on finding from the Women's Health Initiative Observational Study (50-79 years at enrollment and post-menopausal). Among the 93,676 volunteers, only 61,576 participants were in the study cohort, and 429 adjudicated incident ovarian cancer (0.7%). Participants completed annual mailed questionnaires. Participants with bilateral oophorectomy, unknown number of ovaries, history of cancer (except non-melanomatous skin cancers were excluded). Perineal powder exposure (rather than specifically talc use) was obtained via self-report at baseline, and not updated during follow-up. Participants were asked whether powder had been used on genital areas, diaphragm or sanitary napkin or pad. If the participant answered affirmatively, there were further questions regarding duration of use where participants indicate use for less than 1 year, 1-4 years, 5-9 years, 10-19 years, or 20

or more years, but frequency of use was not recorded. The area of use was assessed dichotomously, and duration of use was categorized as never, 9 years or less and 10 years or more for analysis. Analysis was conducted for ever perineal powder use (ever use for any of the three categories) and duration for any powder use (maximum duration of any single area of application). Cancer cases were self-reported and confirmed through medical records including pathology reports. Data on covariates for age, race, education, alcohol, metabolic equivalents, smoking, recreational physical activity, oral contraceptive use duration, hormone replacement therapy, family history, age at last birth, BMI, self-reported family history of ovarian cancer were evaluated. They also evaluated reproductive factors such as age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, hysterectomy, irregular cycles, endometriosis. The covariates were obtained at baseline and not updated. The proportional hazards analysis was conducted to examine the risk of ovarian cancer and proportional hazards was tested using Schoenfied residuals. Participants with other cancers were still considered at risk for ovarian cancer. Covariates were selected for the multivariate analyses, if they had P-values of less than 0.1 during the backward regression until they had a parsimonious model. Additional variables from the literature were also included although they were not statistically significant. They analyzed ever perineal use, perineal use by application area, duration of use and combinations. Test for linear trend was evaluated across duration categories by modeling categories as continuous variables.

The average age of participants was 63.3 years at baseline with 12.4 years of mean follow-up. Most participants were white and were obese. Approximately 52.6% of the population reported ever use of perineal powder. Ever users were more likely to be heavier, used oral contraceptives and/or diaphragms. Perineal use of powder was associated with a 12% excess risk which was not statistically significant ($HR_{adj,}$1.12, 95% CI: 0.92- 1.36) whereas point estimates for use on sanitary napkins and diaphragms were lower than 1 but could not rule out an excess risk. Duration of perineal, sanitary napkin or diaphragms were not associated with ovarian cancer.
Strengths include the prospective design which reduces the risk of recall bias. Limitations includes the lack of information on whether the perineal powder use constituted talc use, and the inability to measure the frequency of exposure. It is possible that the analysis by duration included infrequent long duration users with short term frequent users which may result in bias towards null. Since exposure was not updated during follow-up, some never users who became ever users were misclassified as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer introduced an element of selection bias. Of the initial cohort

of 93,676 volunteers, only 61,576 women were enrolled; 10,622 volunteers who had already developed cancer at baseline were excluded. It is not known whether any (or how many) of these excluded women had ovarian cancer, nor whether any (or how many) were talc users. The inclusion of "prevalent users" rather than "incident users," leads to depletion of susceptibles and may bias findings towards the null. Data on covariates was not available after baseline resulting in the potential inclusion of participants (e.g., oophorectomy) not at risk of ovarian cancer and resulting bias towards the null. The generalizability of the study findings to younger pre-menopausal women is also unknown as the study findings are limited to older post-menopausal women (average age =63.3 years).

IX.III.III. In 2016 Gonzales et al. (93) examined the relationship between douching, talc use, and ovarian cancer among 50,884 women aged 35-74 years of age (84 % white and 64% post-menopausal) who had never had breast cancer but had a full or half-sister who with breast cancer. They excluded participants with bilateral oophorectomy and ovarian cancer. Among 41,654 participants 154 incident ovarian cancers (n=135 ovarian cancers) were reported (0.3%). Participants completed a telephone interview which included questions about reproductive history (oophorectomies), health and lifestyle and use of personal care products before enrollment, including the use of douching and use of genital talc applied as a powder or spray applied to underwear, sanitary napkin, diaphragm, cervical cap, or vaginal area. The frequency of use was categorized as no use, less than once a month, 1-3 times per month, 1-5 times per week, > 5 times per week, but duration of use was not recorded. As with the WHI and Nurses' study exposure was only measured at baseline and not updated during follow-up. Updated information on oophorectomy was collected during follow-up and information on cancer cases was collected via annual health update. Data on 37.6% of ovarian cancer cases was available only by self-report and the remainder confirmed by medical record review or death certificate. Cancer cases included tumors of the ovary, fallopian tubes, peritoneum, or of uncertain origin. Those who were BRCA1 or BRCA 1 positive test or those who had a sister with a positive test but had no report of negative test were considered BRCA positive. Cox proportional hazards analysis was conducted until diagnosis of ovarian cancer, oophorectomy, censoring or death. Generalized estimation equations was used to account for familial clustering at baseline. The proportional hazards assumption was evaluated by the goodness of fit test. A joint analysis of talc and douching use was also conducted. The included covariates were patency (yes or no for tubal ligation or hysterectomy), menopausal status, duration of OC use (none, < 2 2 to <10, 10 or more years), parity (yes/no) race and BMI.

The median duration of follow up was only 6.6 years. The average age was mean 57.8 years for cases. These cases were more likely to have a family history of ovarian cancer and carry a BRCA1 or BRCA2 mutation. More non-cases than cases used oral contraceptives. Talc use was only reported by 12% of cases and 14% of non-cases. Talc users were more likely to have BMI >30 kg/m^2. Talc use in the last 12 months after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status, and patency, was not associated with a statistically significant increased risk of ovarian cancer (HR 0.73, 95% CI: 0.44-1.20], but could not rule out an excess risk. There was no change in estimates when adjusted for douching. Douching at baseline, more common among talc users, was associated with increased risk of ovarian cancer (HR: 1.8 95% CI: 1.2-2.8).

There were significant limitations to the study. The authors acknowledge that an important limitation of their study was that they collected douching and talc information for the year before the study and did not account for the latency. As with the other two cohort studies, the Sister Study was limited by the issue of selection bias through the exclusion of women who had already developed ovarian cancer (and who could also have been lifetime talc users). Secondly, the Sister Study was vulnerable to behavioral change bias. The bias towards the null of this inaccurate assessment of "ever" user status prospectively, at the start of the study, was compounded by the fact that it was also vulnerable to retrospective inaccuracy, because it was based only on the 12 months preceding baseline. Thus, a participant who had last used talc 13 months before baseline would be categorized as a never-user, as would a participant who started using talc after baseline. Thirdly, the Sister Study's median follow-up of only 6.6 years is likely insufficient to detect any risk of ovarian cancer which likely takes more than 6.6 years to develop. The study also suffered from the limitations of prevalent user biases. Additionally, exposure was measured as ever/never use in 12 months prior rather than total applications resulting in non-differential misclassification towards the null. Data was only available by self-report on the diagnosis of ovarian cancer for many cases (37.6%) resulting in misclassification of outcome, which was likely non-differential and may bias findings towards the null. The study reported the lowest rate of talc use among the cohort studies (13.8%), further compounding the limited statistical power due to a short duration of follow-up. The generalizability of these findings is also limited as they included women without breast cancer who all had a family history of breast cancer and may be at a higher risk (60%). The missing data were not missing at random and unclear whether analyses were adjusted for missing data. The authors concluded that the study

could not exclude a increased risk despite these findings. The study findings are limited to the predominant cohort of white post-menopausal women who constituted the majority of participants.

IX. IV. Summary of Findings from Epidemiological Studies.

1. The cumulative evidence from these studies demonstrates a statistically significant increased risk of ovarian cancer associated with perineal talc powder use which has been independently replicated by several investigators in different populations, different settings, across different sources using different study designs and time periods. Slight differences in magnitude of risk among these studies may reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time and some variation due to chance. The updated meta-analyses in 2018, which have included all the studies, reported a statistically significant increased risk of perineal talc use and ovarian cancer, (41, 42), with little evidence of statistical heterogeneity or publication bias. The case-control studies provided 13,421 cases compared to 890 cases in the cohort studies. (42). Most case-control studies demonstrate an increased risk of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors.

2. Meta-analysis which evaluate the association between perineal talc use and ovarian cancer have consistently shown an increased risk of ovarian cancer, (39, 41, 42, 73, 79), including pooled analysis using individual participant data. (10). My conclusions about the causal increase in the risk of ovarian cancer associated with talc exposure are heavily weighted by recent cumulative meta-analysis published in 2018, (41, 42). These meta-analyses provide the most comprehensive evidence base given the size of the study database and their methodologic superiority as assessed by the AMSTAR rating above. (Table 1). Also, importantly, there is no meta-analysis which has reported a statistically significant decreased risk of ovarian cancer with talc.

3. The only case-control study in which point estimates are below one was limited by the poor choice of controls and very high non-response rates. Despite these limitations it could not rule out a 21% increased risk of ovarian cancer associated with talc use which is not inconsistent with other studies. (86). Although the exposure rate to talc in the case-control studies has been variable in the control group from 5%-45%, this reflects the varying practices in the use of talc rather than the lack of an increased risk of ovarian cancer with talc use.

4. Although all studies are at potential risk of outcome misclassification, most of the studies used histologically verification for the diagnosis of ovarian cancer. Any such potential

misclassification of outcomes is likely to be non-differential and would have biased the findings towards the null.

5. There is no reason to believe, from the studies, that ovarian cancer would result in talc use, so the temporality of the association is established.

6. Case-control studies are susceptible to recall bias particularly when data on exposure are self-reported. However, several studies have included these questions on talc exposure as a part of larger questionnaires on other risk factors minimizing the possibility of recall bias. Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures. Further, recall bias is equally likely to affect other histologic types of ovarian (and endometrial) cancer but here the increased risk was limited to only epithelial ovarian cancer in most studies. Finally, the findings that only perineal talc use was associated with ovarian cancer but not with non-genital talc use argues against recall bias alone as a potential explanation of these findings.

7. Confounding is one potential explanation for these findings. However, several case-control studies adjusted for major confounders including the more recent case-control studies. (54). Although residual confounding is always possible in an observational study, studies that have reported adjusted and non-adjusted findings have reported similar results minimizing the impact of residual confounding. (41). Although there are some risk factors for ovarian cancer (e.g., genetic risk factors, family history, obesity and reproductive history), for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. To invalidate the statistically significant findings of an increased risk of ovarian cancer from the studies, one would have to postulate a degree of selection, recall bias and confounding pervasive across different time periods, different populations which is highly implausible.

8. Case-control studies are also at risk of selection bias which may introduce bias in both directions. As opposed to hospital-based controls, which may be less susceptible to selection bias, the population-based case-control studies have consistently showed a higher estimate of increased risk of ovarian cancer associated with talc use.

9. Reverse causality, where the diagnosis of ovarian cancer results in perineal use of talc, may be one possible explanation of the nonsignificantly increased risk in the group exposed to perineal talc. However, this is also likely minimal in the case of ovarian cancer in which most

cases present at advanced stages with abdominal bloating, and vaginal symptoms only occur in a small minority of cases.

10. One of the cohort studies reported an increased risk with perineal talc exposure and serous invasive cancer (14). The pooled results from all three cohort studies, reported an excess risk of ovarian cancer, (42) which failed to reach statistical significance because of several limitations. The duration of follow up was limited resulting in low number of events and inadequate statistical powder. The only cohort study which reported an inverse association between perineal talc use and ovarian cancer included several other cancers beyond the ovary (such as peritoneum, endometrial) (93), which may have diluted an increased risk. It had a very short duration of median follow up of approximately 6.6 years which is insufficient to ascertain the development of ovarian cancer. Since talc induced carcinogenesis occurs via a foreign body mechanism, the latency period required to demonstrate such an effect is long. Despite these limitations, the upper bounds of the confidence intervals exceeded one and could not rule out an increased risk of ovarian cancer with perineal talc use. The cohort studies were at risk of significant other biases. Exposure was measured at baseline and not updated during follow-up (14, 17), which may have misclassified those participants at baseline who were never users but used talc during the study as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer (some of whom may have been exposed to talc) may also bias their findings. (14, 17) The cohort studies were also susceptible to "depletion of susceptibles" biasing their findings towards the null. None of the cohort studies were primarily designed to study the association between genital talc use and ovarian cancer as their primary objective. Despite these limitations, the meta-analysis of cohort studies demonstrated a statistically significant increased risk of serous invasive ovarian cancer.

11. Ascertaining *dose response* relationship with talc and ovarian cancer is difficult because of the challenges in quantifying talcum powder use usually collected by self-reported data (frequency, amount and duration), timing and patterns of use (e.g. douching), and other individual factors (e.g. co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. The dose response depends on both the amount of talc exposure, the frequency of talc uses and the duration. It is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an ''application of talc.' Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open, the age of initiation of talc use since the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (79). The presence of other risk factors

such as post-menopausal status, cancers other than invasive serous ovarian cancer may make it difficult to ascertain a dose-response relationship among older post-menopausal. The lack of statistical trend (58, 60) in some earlier studies may reflect some of these challenges as well the lack of a monotonic dose response effect. The exposure-response data need to be interpreted in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer in susceptible individuals through accelerating the redox state in epithelial ovarian cancer cells. (49). Thus, an assessment of the gradient through a monotonic dose-response curve may not provide a complete picture of the biological gradient. It unclear why nature would mandate an increasing mono-tonic dose-response mechanism for causation, and some have argued that among Bradford-Hill viewpoints it is difficult to know how dose-response should be modelled. (50). Cumulative lifetime exposure may be a more appropriate measurement of exposure given the inflammatory mechanisms by which talc induces the development of ovarian cancer. It is important to recall that if the carcinogenicity of talc induced ovarian cancer most likely resembles that of asbestos induced mesothelioma (with which it shares histologic similarities), asbestos induced mesothelioma does not have a dose-response relationship. In the case of asbestos induced mesothelioma, latency may be more important whereas in the case of talc induced ovarian cancer induced by inflammation latency may be of lesser importance.

12. Despite these challenges, several studies have shown evidence of dose-response as measured by an increased risk with increased frequency (51-55) or increased duration, (52, 54)or combination of frequency and duration of exposure. (48, 54). Some studies show a exposure-response trend, (54) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). In the individual participant data meta-analysis a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis, but no significant trend was seen when analyses were restricted to ever users. (10) Importantly, the most recent meta-analysis reported an evidence of dose-response with risk being higher among those with >3600 applications of talc compared to participants with <3600 applications. (42) Both of these categories of exposure were associated with an increased risk of ovarian cancer. None of the cohort studies were able to conduct meaningful dose-response analysis because they did not collect data either on duration, (14, 93) or frequency of exposure. (17).

X. BIOLOGICAL MECHANISMS OF TALCUM POWDER INDUCED OVARIAN CANCER.

Although not an absolute requirement for determination of causation there are multiple well-established biological and molecular mechanisms by which talcum powder products induce ovarian cancer. The key routes of exposure and biological mechanisms are noted below.

X.I. Retrograde Migration of Talc Particles. Genital talc can migrate up to the fallopian tubes and ovaries and talc particles have been detected within the ovaries of women who report perineal talc use. Heller et al. detected talc in the ovaries of 24 women undergoing incidental oophorectomy demonstrating that it can reach the upper genital tract (64) although the fact that talc particle counts were unrelated to reported levels of perineal talc exposure reflects the challenges in measuring exposure to talc. Talc has been found deeply embedded within ovarian tumors, (65) and subsequent studies have confirmed that these are not due to contamination. (94). Talc has also been demonstrated in pelvic lymph nodes of women with perineal talc exposure.(66). Supportive evidence of migration comes from studies showing retrograde migration of additional particles such as starch after gynecological examination, (68) findings of a decreased risk of ovarian cancer with tubal ligation and hysterectomy in case-control studies, (87) and meta-analysis, (115) which may minimize exposure to inflammatory particles. Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of "measurable quantities of talc' in monkey models, (67) the timing and techniques of assessment and intraspecies differences could not rule out migration of talc particles. The FDA response to Citizen's Petition 2014 concluded the *"potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable'*. Johnson & Johnson and IMERYS documents also acknowledge migration. In one document it was stated, "A review of the literature suggests that it is biologically plausible for talc particles to migrate from the vagina to the peritoneal cavity and ovaries following perineal application." (63, 116).

X.II. Inhalation of Perineal Talcum Powder. Inhalation of talcum powder is another potential route of exposure that is biologically plausible and can cause inhaled fibrous talc (and asbestos) fibers to reach the ovary and thus increase the risk of ovarian cancer in women using these products. Approximately 50 percent of talc particles in commercially available talcum powder are less than 10 microns in size, (117) which have the potential for inhalation and reach the alveolar regions of the respiratory tract. (118) Asbestos fibers can pass from the alveoli to the

lung interstitium, from which they can travel via the lymphatic system to the bloodstream and other organs including ovaries. (119, 120) Inhaled fibrous talc shares extensive physical and chemical similarities with asbestos, and inhaled fibrous talc generated from perineal application may also reach the ovaries by inhalation. This mechanism was confirmed in a September 2017 study, "Below the Waist Application of Johnson & Johnson Baby Powder," Longo, et al. showed that normal application of Johnson's Baby Powder can produce airborne asbestos and talc fibers which could be inhaled. (70).

X.III. Talcum Powder Induced Inflammation and Alteration of Redox Potential. Inflammation has long been understood to be an important mechanism underlying the development of ovarian cancer. (61). Inflammation may underlie ovulatory events because an inflammatory reaction is induced during the process of ovulation. Risk factors for ovarian cancer include endometriosis (i.e., ectopic implantation of uterine lining tissue) and pelvic inflammatory diseases (PID). (121). PID was associated with an increased risk of borderline ovarian tumors, particularly among women who had had multiple episodes of pelvic inflammatory disease in a meta-analysis. (122). Consistent with the inflammatory mechanism for ovarian cancer, a prospective nested case-control study from the Prostate, Lung, Colorectal and Ovarian Cancer has also shown that global markers of inflammation such as C-reactive protein, Interleukin L-1α, Interleukin-8 and Tumor Necrosis Factor-α are associated with a significantly increased in the risk of ovarian cancer. (123). Supportive evidence for the role of inflammation also comes from a meta-analysis showing a decreased risk of ovarian cancer with tubal ligation and hysterectomy. (115). Studies have demonstrated increased risk of ovarian cancer with talcum powder use, and increased risk of ovarian cancer with endometriosis. (87). This risk is 3-fold higher among women exposed to talc who have endometriosis. (48).

Oxidative stress in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays a role in the pathogenesis, neo-angiogenesis (formation of new vessels) and the dissemination of both early and late stage epithelial ovarian cancer. (124, 125). Epithelial ovarian cancer cells manifest a persistent pro-oxidant state characterized by upregulation of certain key oxidant and downregulation of key antioxidant enzymes, (125) and the presence of oxidative stress triggers cancer cells to favor anaerobic metabolism. Oxidative stress induces phenotypic modification of tumor cells by altering cross-talk between tumor cells and surrounding stroma. Talc can alter this redox state and cause a marked increase in mRNA levels of the prooxidant enzymes, iNOS (nitrous oxide) and MPO (myeloperoxidase) in talc treated ovarian cancer cells as compared to control as early as 24 hours in all doses, (49) as well as a marked decrease in the

mRNA levels of the antioxidant enzymes catalase CAT, glutathione peroxidase (GPX), and superoxide dismutase (SOD3) providing a mechanism by which talcum powder products can induce the development of ovarian cancer.

Cancer antigen [CA-125] a tumor marker secreted by the epithelial cell for monitoring recurrence after treatment of ovarian cancer, was elevated when both normal ovarian cell lines [1.7 +/- 0.5-fold] and ovarian cancer cell lines [1.4±0.5 and 4.4±0.5-fold increase in OV90 and TOV-21G EOC cell lines] were exposed to talc, providing another molecular mechanism by which talc can increase the risk of ovarian cancer. (106).

Talc has been shown to increase proliferation, induce neoplastic transformation and increase ROS generation time-dependently in the normal human epithelial and granulosa ovarian cells and dose-dependently in the polymorphonuclear neutrophils. (71). In studies of human mesothelial cells, both nonfibrous talc and asbestos have shown evidence of genotoxicity. (109) Some have suggested that perineal talc use may also increase risk of ovarian cancer by the induction of anti-MUC1(monoclonal antibodies) possibly via heat-shock protein, (72) although the data are not definitive. (101).

X.IV. Carcinogenicity in Animal Studies. Among animal studies a study among rats demonstrated the development of papillary changes after intrabursal injection of talc. Such papillary changes may be precursors of serous papilloma precursors of epithelial cancers. (107). Another 2-year inhalation study with cosmetic grade talc in rats and mice showed evidence of carcinogenic activity in male (an increased incidence of pheochromocytomas of the adrenal gland) and female (increased incidences of alveolar/bronchiolar adenomas) rats and carcinomas of the lung and pheochromocytomas of the adrenal gland. (108). There was no evidence of carcinogenicity in mice. However, limitations of this study include the lack of a suitable control (e.g. titanium dioxide), alternative explanations of these findings via particle overload, (127) and the fact that ovulatory patterns in rats are not fully applicable to humans.

X.V. Presence of Asbestos and other carcinogens in Talcum powder products. In assessing the biological plausibility of talcum powder products as a cause of ovarian cancer, it is important to consider the constituents of talcum powder products including whether it contains known or suspected carcinogens. The presence of asbestos in talcum powder products can and does provide a plausible biological explanation of the development of ovarian cancer. (36, 37).

Occupational exposure to asbestos is a well-established causal agent for the development of pleural and peritoneal mesothelioma, larynx and ovarian cancer. (36, 127). Talc and asbestos also share chemical similarities. The carcinogenicity of asbestos relies on shape of particles with long thin fibers-such as those occurring in crocidolite asbestos being particularly carcinogenic. Although talc consists primarily of platy talc, it may also contain fibrous talc or other asbestiform minerals. Epithelial ovarian cancer, one most closely associated with talc, histologically most closely resembles mesothelioma providing further evidence of biological mechanisms. As Huncharek notes in their meta-analysis of ovarian cancer associated with talc dusted diaphragm meta-analysis on page 427 "*If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogen effect as it contains a known carcinogen.*" (13). In addition talcum products contain fibrous talc, heavy metals and fragrance ingredients which are known or suspected carcinogens. (26, 33, 35, 36). Like the presence of Asbestos Fibers, the presence of these known or suspected carcinogens provide a plausible biologic explanation for the increased risk seen in the epidemiologic studies.

XI. ASSESSMENT OF CARCINOGENECITY OF TALC BY THE IARC IN 2006.

The International Agency for Research on Cancer (IARC) expert panel evaluates the carcinogenicity of various products using the following criterion after review of animal studies, experimental studies and epidemiological data. (128). The data is examined to determine whether there is *sufficient evidence, limited evidence, inadequate evidence, or evidence suggesting lack of carcinogenicity* for both cancer in humans and animals, respectively. The mechanistic and other relevant data are examined to *identify established and likely mechanisms and determines whether each mechanism could operate in humans*. The agents are then classified into several groups. Group 1 are agents *carcinogenic* to humans (e.g., asbestos,) (37), Group 2A are agents *probably* carcinogenic to humans, Group 2B *possibly* carcinogenic to humans, Group 3 agents which are *unclassifiable* and Group 4 agents which are *probably not carcinogenic* to humans.

In 2006 IARC concluded that perineal use of talc not containing asbestos or asbestiform fibers was possibly carcinogenic to humans (129) based on *limited evidence in humans for the carcinogenicity of perineal use of talc based body powder and the limited evidence in experimental animals for the carcinogenicity of talc* (93) (Group 2B-b). (38). Although a positive association has been observed between exposure to the agent and cancer for which causal interpretation is considered by the Working Group to be credible, but chance, bias, or confounding could not be ruled out

with reasonable confidence. For purposes of their evaluation, IARC considered 19 case-control studies and 1 cohort study. (14). The Working Group concluded that 8 of the more informative case-control studies (as well as most of the less informative ones) showed a consistent excess risk in the order of 30-60%. The cohort studies neither supported or refuted the evidence from case-control studies.

The IARC assessment was carried under the assumption that talcum powder products did not contain asbestos based on the published findings at the time- an assumption that is not supported by current data. In such a case, talcum powder products would be unequivocally classified as a Group 1 carcinogen like asbestos. Importantly, even absent a finding of asbestos in talcum powder products, the consistent cumulative evidence of peritoneal use of talcum powder products demonstrates an increased risk of ovarian cancer. Several *new systematic reviews based on recently published studies have further added to the accumulating evidence on an increased risk of ovarian cancer with talc use.* (10, 41, 42). *There is now further evidence of exposure response* relationships, with measured by an increased risk with increased duration (52, 54) or combination of frequency and duration (48) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). Finally, in addition to the epidemiologic evidence there is evidence from toxicology , molecular biology and other mechanistic data which supports my opinions .

XII. COSMETIC EXPERT REVIEW PANEL REPORT.

For the sake of completeness I also reviewed a report on the safety of cosmetic talc by an industry sponsored panel. (130). The panel was primarily composed of dermatologists, with limited expertise in epidemiology and carcinogenicity. The review was carried out under the flawed assumption that cosmetic-grade talc must contain no detectable fibrous, asbestos minerals and thus limited its assessment to animal and clinical studies on talc that did not contain asbestos, and erroneously concluded that there was no evidence of talc migration. As a result of these serious methodologic shortcomings and funding biases it arrived at its erroneous conclusions that talc was safe for use in cosmetics. (130) As discussed above, the findings of this panel have been superseded by findings from several new epidemiological studies, mechanistic studies and systematic reviews which have further added to the accumulating evidence on an increased risk of ovarian cancer with talcum powder product use.

XIII. ASSESSMENT OF CAUSALITY.

While talc is clearly associated with development of ovarian cancer, we must assess whether the observed association leads to an inference about causation. In 1965, in the President's Address to the newly-established Section of Occupational Medicine of the Royal Society of Medicine, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics at the University of London, attempted to encapsulate the aspects of a causal relationship, as it was understood at the time. (1). As he described them, they were: 1. strength of association, 2. consistency, 3. specificity, 4. temporality, 5. biological gradient, 6. plausibility, 7. coherence, 8. experiment, and 9. analogy. As Professor Hill explained, no aspect alone is either necessary or sufficient: "What I do not believe . . . is that we can usefully lay down some hard-and-fast rules of evidence that ***must*** be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence . . . and none can be required as the ***sine qua non***." Further, according to Professor Bradford Hill, these are not the only aspects of causation, but they are informative. It must also always be remembered, as highlighted in a recent statement by the American Statistical Association, that a lack of statistical significance does not imply lack of clinical significance (18) – a point also highlighted by Bradford Hill, who noted that while statistical tests can remind us of the role of chance, *"No formal tests of significance can answer those questions."*

With respect to the analysis at issue, that is, the association between talcum powder products and ovarian cancer—the results are not only statistically significant, but, as described above, have been replicated by several independent authors in multiple studies across a range of study designs. The cumulative body of evidence was appraised using the Bradford Hill viewpoints. In this regard, and as described in this report, I put significant weight on the Strength, Consistency, Temporality, Biologic Plausibility, and coherence factors and, to a lesser extent, Gradient (Dose-Response) and Analogy data to support my opinion that Talcum Powder Products can cause ovarian cancer. For the reasons stated below, I do not weigh heavily the Experiment and Specificity data in light of the totality of the evidence supporting a causal inference. My assessment is described below.

1. Strength of Association. This aspect of a causal relationship refers to the degree or magnitude of effect to which the exposure is associated with the outcome. (1). According to Bradford Hill , the more likely the exposure is associated with the outcomes, the more likely is it to be causal. As summarized in the meta-analysis in section above, I conclude that the association of talc with

ovarian cancer shows an approximate 30-60% relative increase in the risk of ovarian cancer, after adjustment for multiple confounders of the talc and ovarian cancer relationship. (10, 42). The strength of the association, replicated in multiple studies, provides evidence in support of a causal association**.** There are several noteworthy examples of well-established causal relationships (e.g. second hand smoking and lung cancer), (131) where the strength of the association is in the order of 20-40%. Such causal associations can have significant effects on the population if a large segment of the population is exposed, as in the case of air pollutants and myocardial infarction, which are significantly associated with an increase in MI risk with small relative risk (carbon monoxide: 1.048; 95% CI, 1.026-1.070; nitrogen dioxide: 1.011; 95% CI, 1.006-1.016; sulfur dioxide: 1.010; 95% CI, 1.003-1.017; PM_{10}: 1.006; 95% CI, 1.002-1.009; and $PM_{2.5}$: 1.025; 95% CI, 1.015-1.036) but a large population burden because of the large percentage of the population that is exposed. (47). Similarly, 75-100 mg of daily Aspirin has been shown to reduce the risk of cardiovascular events among those weighing 50-69 kg by 25 % [HR 0.75, 95% CI, 0.65-0.5] (132) in an individual participant data meta-analysis of randomized controlled trials. An increment of one serving a day of fruit and vegetables reduced all-cause mortality by 5% (HR 0.95 95% CI: 0.92 - 0.98) in a meta-analysis of cohort studies. (133). As discussed below, I place significant weight on the fact that studies demonstrate a strong association between talcum powder use and ovarian cancer and show consistency of the data.

2. Consistency. This viewpoint assesses whether the finding is repeated in different settings, place and time. (1). As shown in detail above, the direction and strength of association of talc and ovarian cancer is generally consistent across studies, including observational studies of various designs and their meta-analysis, and observational studies. These studies have been conducted in different clinical settings across the world, with different duration of follow up and the cumulative evidence has consistently shown a significantly increased risk of ovarian cancer with the use of talcum powder products. As expected, there are slight differences in the point estimates which reflect differences in study population with nearly all point estimates showing a direction of increased risk of ovarian cancer. The confidence intervals, however, across study designs overlap, indicating consistent results. I place significant weight on the fact that the consistency and strength of the association found in multiple independent studies demonstrates that the association is causative.

3. Specificity. This viewpoint considers whether the outcome of the disease appears to be specific to the exposure, (1) although since the original publication of the Bradford Hill we know

in most cases, absolute specificity for an exposure outcome association is not generally possible for many diseases, particularly cancer, and not required to provide proof of causation. Even the well-established, causal relationship between cigarette smoking and lung cancer or heart disease is not characterized by specificity. Genetic factors may also play a role in the occurrence of ovarian cancer. As discussed above, the occurrence of ovarian cancer is consistently higher among talcum powder users compared to non-users, even after adjusting for several confounders. I placed less weight on absolute specificity of the association between talcum powder exposure and ovarian cancer given the multi-causal nature of the outcome, particularly in light of the strength and consistency of association factors.

4. Temporality. The temporality viewpoint assesses whether the exposure always predates the development of disease. (1). In each of the epidemiologic studies noted above, talc exposure occurred before the diagnosis of ovarian cancer. Although some have argued that some of the symptoms of ovarian cancer (vaginal bleeding, irritation) may lead to talcum powder use, since most ovarian cancers present with abdominal bloating and advanced stages of the disease it is difficulty to attribute how development of ovarian cancer would lead to talc use (e.g., reverse causality). I placed significant weight that the exposure to talc preceded the development of ovarian cancer in the studies above.

5. Biological Gradient. This viewpoint assesses whether there is a biological gradient or dose-response effect, (1) recognizing that presence of dose-response is not an absolute requirement for causation. In order to determine dose-response, it is necessary first to determine dose. While the presence of a dose-response relationship supports a causal link, the absence of such a relationship does not preclude a causal association. The causal relationship between asbestos and mesothelioma, which most closely resembles the current scenario is not dose-dependent. Assessing dose-response is challenging in the context of perineal talc use for several reasons: first, unlike, say, birth-control pills, the amount of talc powder product use is not fixed, nor is the number of uses per time (day, week, or month). At a minimum, to assess total dose, it is necessary to acquire information about both duration and frequency. Ascertaining a dose-response relationship with talc and ovarian cancer is particularly challenging given that the risk of ovarian cancer may vary with age, premenopausal and post-menopausal status and the presence of other risk factors. The dose-response depends on both the amount of talc exposure, the frequency of talc uses and the duration. The presence of other risk factors such as post-menopausal status, cancers other than invasive serous ovarian cancer and the "depletion of

susceptibles" over time may make it difficult to ascertain a dose-response relationship. Several studies show evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 54). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis show evidence of duration dose and responsiveness, (42) with risk being higher among those with >3600 applications of talc compared to participants with < 3600 applications, although with overlapping confidence intervals. (42). Based on the above limitations with study design to ascertain dose effect, specificity of dosing of talc and the possibility of threshold effect, I find biological gradient less compelling, but still compelling of my causation analysis than the other Bradford Hill overviews as referenced above.

6. Plausibility. Although this is not a requirement for causation, an association that is biologically plausible is more likely to be causal. (1). While this viewpoint only requires biological mechanism to be *plausible*, which is necessarily limited to the state of biological knowledge at the time of assessment, evidence from the literature described in detail in the section in biological mechanisms shows multiple routes of exposure, multiple pathways and multiple mechanism by which talc can cause ovarian cancer. **Section X** demonstrates how talcum powder products can migrate to the ovaries, induce inflammation, alter redox potential resulting in a pro-oxidant state, (49) and act as a mutagen. (109). As a results of the significant body of evidence that has accumulated on biological mechanisms, I place significant weight on the fact biological plausibility provides evidence in support of the causal role of talc in the development of ovarian cancer and there is a highly biological plausible mechanism here for carcinogenicity which supports my opinion.

7. Coherence. This viewpoint assesses whether the cause-and-effect interpretation of data conflicts with the generally known facts of the natural history and biology of the disease. (1). The evidence on the risk of ovarian cancer with talcum powder exposure is consistent with the nature of the disease. Multiple studies suggest that talcum powder products have biological effects which plausibly explain the occurrence of ovarian cancer. Given the biological mechanisms related to inflammation described above, this mechanism and causal association itself fit easily within the current framework of scientific knowledge about the development of

ovarian cancer mediated by inflammation. I placed a significant weight on the coherence of findings in support of the causal role of talc in the development of ovarian cancer.

8. Experiment. Occasionally, in making a causation assessment, it is possible to appeal to experimental, or semi-experimental, evidence. The definitive experimental evidence would be a placebo controlled randomized trial among patients who are assigned to use talc and others who do not use talc in which the outcome of incident ovarian cancer would be actively ascertained. However, such evidence does not exist and would not be ethical nor feasible with a rare outcome such as ovarian cancer with an incidence of 11.4/100, 000 person-years noted above. While there is no randomized controlled trial here, that is common when dealing with a suspected cancer risk. For instance, there is no randomized controlled trial which supports the causal role of smoking in lung cancer. Such a trial to provide absolute proof of harm, which ignores the body of evidence that has accumulated and places patients at risk for developing ovarian cancer raises significant ethical concerns when data from robust observational studies and their meta-analysis have consistently shown an increased risk of ovarian cancer. In the absence of experimental evidence, this overview is weighted as less important than the other more important viewpoints noted above.

9. Analogy. Asbestos has been shown to cause ovarian cancer which offers an appropriate analogy, (40) but this viewpoint was considered less significant than other viewpoints noted above.

XIV. CONCLUSIONS.

Based on my background, training and education as a physician and epidemiologist, review and analysis of the totality of the evidence, using the weight of evidence analysis, including considering and weighting the Hill viewpoints, as described in this report, it is my opinion stated to a reasonable degree of scientific and medical certainty that peritoneal use of talcum powder products can cause ovarian cancer.

Signed this 16th day of November 2018

Sonal Singh, MD, MPH

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Table 1. AMSTAR (Assessing the Methodologic Quality of Systematic Reviews) Rating of Systematic Reviews and/or Meta-analysis of Genital Talc use and Ovarian Cancer

Criterion	Harlow et al 1992[1]	Gross and Berg et al 1995[2]	Cramer et al 1999[3]	Huncharek et al 2003[4]	Langseth et al 2007[5]	Terry et al 2013 #[6]	Berge et al 2018[7]	Penninkilampi and Eslick 2018.[8]	Huncharek et al 2007 9*
A priori design	UA	Y	N	UA	UA	Y	Y	Y	UA
Duplicate study selection & extraction	N	N	N	Y	N	NA	Y	Y	Y
Comprehensive search	N	N	N	UA	N	NA	Y	Y	N
Status of publication used as criterion	UA	N	UA	Y	UA	NA	Y	N	Y
List of included & excluded studies	N	N	N	N	N	Y	Y	Y	N
Characteristics of studies provided	N	Y	N	N	N	Y	Y	Y	Y
Scientific quality of studies addressed	N	UA	N	N	Y	Y	Y	Y	N
Scientific quality of studies used in formulating conclusions	N	Y	UA	N	Y	Y	Y	Y	N
Methods of combining studies appropriate	N	Y	Y	Y	Y	Y	Y	Y	N
Likelihood of publication bias addressed	N	N	N	N	N	NA	Y	Y	N
Conflict of interest included	Y	Y	Y	UA@	Y	Y	Y	Y	UA@

*Meta-analysis by Huncharek et al in 2007 et al evaluated only talc on contraceptive diaphragms

Terry et al 2013 conducted an individual participant data pooled analysis so several items for systematic review NA

@ Incomplete financial disclosures of role of sponsor in meta-analysis

Y= Yes N= No; NA= Not applicable; UA : Unable to answer

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Additional Materials and Data Considered

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Other Materials

1. WCD000254-WCD000255
2. IMERYS210136-IMERYS210137
3. IMERYS241994-IMERYS242004
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8. JNJ000251888-JNJ000251890
9. JNJ000261010-JNJ000261027
10. JNJ000460665-JNJ000460673
11. JNJ000526231-JNJ000526676
12. JNJAZ55_000000577-JNJAZ55_000000596
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17. JNJMX68_000004996-JNJMX68_000005044
18. JNJNL61_000001534-JNJNL61_000001535
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EXHIBIT A

Sonal Singh, MD MPH
55 Lake Ave North
Worcester, MA 01655-0002 USA
Tel: 774 442 6611.
Sonal.Singh@umassmemorial.org

Education

MPH, Bloomberg School of Public Health, Johns Hopkins University
Baltimore, MD 6/2005 to 5/2008

Internal Medicine Residency, Unity Health System, affiliate University of Rochester
Sch of Medicine and Dentistry, Rochester, NY 7/2002 to 6/2005

MD, Patna Medical College, Patna, India 12/91 to 05/1999

Academic Appointments

Associate Professor, Department of Family Medicine & Comm Health 10/2016 to date
Department of Medicine, University of Massachusetts Medical School

Assistant Professor, Dept of Medicine, Johns Hopkins Univ SOM 7/2009 to 9/2016

Assistant Professor, Center for Public Health and Human Rights
Bloomberg School of Public Health, JHU (joint) 7/2009 to 9/2016

Assistant Professor, Department of Medicine, Wake Forest University 7/2007 to 6/2009

Instructor, Department of Medicine, Wake Forest University 7/2005 to 06/2007

Employment History

Associate Professor, Department of Fam Medicine & Comm Hlth 10/2016-present
Meyers Primary Care Institute & Department of Medicine (Joint)
University of Massachusetts Medical School
Role: Clinician- Investigator

Associate Professor, Department of Quantitative Health Sciences 10/2018-present
University of Massachusetts Medical School
Role: Clinician- Investigator

Assistant Professor, Dept of Medicine, Johns Hopkins University. 7/2009 to 9/2016
Role: Clinician- Investigator

Assistant Professor, Department of Medicine, Wake Forest University 7/2007 to 6/2009
Role: Clinician- Educator

Instructor, Department of Medicine, Wake Forest University 7/2005 to 6/2007

Role: Clinician- Educator

Residency (Medicine) Unity Healthy System, affiliate of the University of Rochester, Rochester, NY 7/2002 to 6/2005

Role: PGY 1, PGYII and PGY III Internal Medicine Resident

Research Associate, Clinical Pharmacology, Ohio State University 3/2001 to 6/2002
Role: Research assistant in clinical trials

Voluntary Research Associate, Clinical Pharmacology, Ohio State University 8/2000 to 2/2001
Role: Research assistant in clinical trials

USMLE STEP 1, II, III and Clinical Skills Exam Preparation 2/2000 to 7/2000
Role; Medical student

Resident, Medicine, Patna Medical College, Patna, Bihar, India 2/1998 to 1/2000
Role: Junior Resident in Medicine

Compulsory rotatory internship, Patna Medical College, Patna, India 12/97 to 12/98
Role: Fulfilling requirements for completion of medical degree in India

Certification and Licensure

Diplomate, American Board of Internal Medicine 8/2005-12/25

Massachusetts Board of Physicians 8/2016-8/2019

Physicians and Surgeons of Maryland (Inactive) 2009-2017

North Carolina Medical Board (Inactive) 2005 to 2009

Professional Memberships and Activities

Massachusetts Medical Society 2017-current

American College of Physicians 2003-2019

International Society of Pharmacoepidemiology 2011-current

Society of General Internal Medicine 2003 to 2016

International Society of Pharmacoeconomic Outcomes Research 2016 to 2017

Academy Health 2013

Global Health Council 2006 to 2010

Honors and Awards

Finalist W. Leigh Thompson Excellence in Research: Faculty Award, JHU 2016

Visiting Professor, Department of Medicine, Univ of Alabama 2013

3rd Best Abstract (trainee) 29th ICPE Montreal, Canada 2013

Bruce Squires Award for the Best Research Paper, CMAJ 2011

Scholars Abstract Award, Society for Clinical and Translational Sciences. 2010

Society of General Internal Medicine Clinical Investigator Award (Mid-Atlantic) 2010

Elected, Delta Omega Honorary Public Health Society, Johns Hopkins University 2008

Master Teacher Award, WFUSOM 2008

Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM 2007

Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM 2006

Senior–Resident Scholarship award, Unity Health System, NY 2005

ACP Health and Public Policy Scholarship, NY 2005

Committee Assignments and Administrative Services

American College of Physicians, Massachusetts Chapter, Health Policy Committee 2018

Chairs Advisory Council, Department of Fam Medicine & Comm Hlth 10/2016-present

American College of Chest Physicians, Cough Guideline Expert Panel 2017- present

Associate faculty, Welch Ctr for Prevention, Epi & Clin Research, JHU 2015 to 2016

Associate-Director, Center for Drug Safety and Effectiveness, JHU 2013 to 2016

Affiliate faculty, Center for Hlth Services and Outcomes Research, Johns Hopkins Bloomberg School of Public Health 2012 to 2016

World Health Organization, International Agency of Research on Cancer (IARC) Monograph- 108 Working group, Lyon, France. 2013

Preferred Items for Reporting of Systematic Reviews and Meta-analysis of harms Working Group Alberta Canada. 2012

Member, Health & Human Rights Working Group, JHU Center for Aids Research 2012

Core faculty, Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2009 to 2016

Core faculty, Evidence-Based Practice Center, JHU 2009 to 2016

Medical Director, Outpatient Clinic, WFUSOM 7/2005-6/2009

Teaching Activities

Classroom

Comparative effectiveness research (2 cr), Johns Hopkins Medicine 2015 to 2016
Role: Developed course in CER for MD and MD/PhD trainees in the CTSA

Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2011 to 2015
Role: Annual lecture in the course for MPH students

Health Economic, Johns Hopkins Bloomberg School of Public Health 2013
Role: Annual lecture in the course for master's students

Pharmacoepidemiology, Johns Hopkins Bloomberg School of Public Health 2011-2015
Role: Annual lecture in the course for Masters and Doctoral students

Evidence-based Medicine, Johns Hopkins University School of Medicine 2012
Role: Course facilitator

Intro to Clinical Investigation, Johns Hopkins University School of Medicine 2012
Role: Annual lecture in the course

Clinical Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2010-2014
Role: Annual lecture in the course

Patient Physician and Society, Johns Hopkins University School of Medicine 2009
Role: Course facilitator

Clinical Teaching

Outpatient medicine 2016-2018

Role: Precepting residents and medical students in clinic at University of Massachusetts Medical School

Evidence Based Medicine 2012-2014
Role: Developed a novel course to teach Evidence based Medicine to Osler medical residents at Johns Hopkins University School of Medicine

Outpatient medicine 2005 to 2009
Role: Precepting residents in clinic at Wake Forest University

Inpatient Medicine 2005 to 2009
Role: Precepting internal medicine residents at Wake Forest University

Trainee /Junior Faculty Name	Mentoring Role	Title of Research Project/Paper	Current Position and Institution	Training Period
Univ of Massachusetts				
Mayuko Itofukunaga, MD	Faculty mentor	Systematic review of decision aids for lung cancer screening	Assistant Professor-Pulmonary Medicine and Critical Care	2017-18
Nathaniel, Erskine MD, PhD (student)	Scholarly activity	SR of herpes zoster and cardiovascular disease	MD/PhD Student Umass Med School	2017
Richeek Pradhan MS	Scholarly activity	Comparison of data on Adverse events	Phd Student McGill University	2017-18
Johns Hopkins Univ				
Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student	2018
Geetha Iyer, MD	Faculty mentor	Multiple Pharmacoepidemiologic studies	Doctoral student, HSPH	2015-16
Sathiya Priya Marimathu	Faculty mentor	Generic drugs and patient oriented outcomes	MHS Student, JHMI	2015-16
Yohalakshmi Chelladurai, MD, MPH	RA Scholarly activity	Review of varenicline	Resident physician, Mercer, Atlanta	2013
Hsien-Yen Chang PhD	Faculty mentor	Pharmacoepidemiologic studies	Assistant Scientist at JHU	2011-15
Hasan Shihab, MD, MPH	RA Scholarly activity	Review of GLP-based therapies	Resident, Franklin Square, Baltimore	2013-14
Joshua Sclar, MD, MPH	Scholarly activity	Systematic review of attacks on health workers	General Preventive Medicine Resident	2013
Crystal Ng, MPH	Scholarly activity	Human Rights measures	MPH Student, JHSPH	2013
Ekta Agarwal, MPH	Capstone	Safety of novel anticoagulants	MPH student JHSPH	2013
Meijia Zhou, MHS	Scholarly activity	Adherence to novel anticoagulants	Doctoral student, Univ of Pennsylvania	2013
Kaitlin Hayman, MD	Capstone	SR of the impact of disasters On CVD outcomes	MPH student, JHSPH	2013
Wenze Tang, MPH	Scholarly activity	SCCS analysis of GIB bleeding with dabigatran	Doctoral student, HSPH	2013

Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student JHSPH	2018
Shabana Walia MD	Scholarly activity	SR of CVD among refugees and displaced	ER physician, UT Houston	2016-2018
Wake Forest Univ				
Aman Amin, MD	Resident	Inhaled corticosteroids and pneumonia	Practicing internist, NC	2007-09
Apurva Trivedi, MD	Scholarly activity	SSRIs and bleeding	Gastroenterologist	2007-09
Other institutions				
Tonya Breaux-Shropshire PhD, MPH	Scholarly activity	Systematic review	Post-doctoral trainee, UAB	2015
Abhay Kumar, MD	Resident Scholarly activity	Wernicke encephalopathy after gastric bypass: systematic review	Assistant Professor St Louis University	2007

Current Grants and Contracts

Grants

(Ming Tai-Seale) 2/2016-12/2021
PCORI
Improving Patient-Centered Communication in Primary Care: A Cluster Randomized Controlled Trial of the Comparative Effectiveness of Three Interventions
The aim is to compare three interventions to improve patient communication in primary care
Role: co-investigator

(PI Jerry Gurwitz) 08/2018- 09/2019
NIH/NIA-1 R56 AG061813-01
Project Title: Controlling and Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)
Role : co-investigator
The aim is to develop interventions to prevent prescribing cascades among those with Alzheimer's related Dementia (ADRD)

Past Grants

Death Data Exploration 08/01/17- 03/02/18
FDA Foundational Elements 3 HHSF223200910006I
Task Order Number: HHSF22301012T
Efforts to Develop the Sentinel Initiative HHSF223200910006I.
Role (Project Lead)

Effect of Therapeutic Class on Generic Drug Substitutions. 2014-2016
U01FD005267-01 (PI, Jodi Segal)

FDA 349,480
Role: Co-Investigator 0.6 CM

Comparative effectiveness Research & The Cochrane Eyes and Vision Group 2013-2016
U01 EY020522 (PI, Kay Dickersin)
NIH/NEI 825,397
Role: Co-Investigator 2.4 CM

Systematic review of gabapentin for neuropathic pain using multiple data sources 2015-2016
(PI, Caleb Alexander)
FDA Center of Excellence in Regulatory Science
Role: Co-Investigator (20% effort)

Integrating multiple data sources for meta-analysis to improve patient-centered outcomes research 2014-2016
(PI- Dickersin)
PCORI (ME-1303-5785) $698,174
Role: Advisor (2% effort)

Development of a scale for human rights violations. 2013-2014
(PI, Chaisson & Beyrer)
NIH Johns Hopkins Center for AIDS Research $ 18,873
Role: Pilot Awardee

Comparative effectiveness review of therapeutic options for obesity in the Medicare population.
Johns Hopkins Evidence Based Practice Center. 2013-2014
PI (Eric Bass)
AHRQ $125,000
Role: Project Principal Investigator (20% effort)

Center for Excellence in Comparative Effectiveness Education 2012-2013
PHRMA Foundation (PI Jodi Segal) Total Direct Cost: $250,000
Role: Co-investigator (5% effort)

A multi criteria decision analysis to assist with regulatory decisions around benefit and risk
Partnership in Applied Comparative Effectiveness Science: 2010 to 2013
PI (PI, Jodi Segal).
FDA $3,509,657
Role: Project Principal Investigator (25% effort)

Combination therapy vs. intensification of statin mono-therapy: An update. 2012-2013
PI (E. Bass- P.I of EPC.)
AHRQ
Role: Advisor (5% effort)

Troponin cardiac marker during renal impairment. 2012-2013
(E. Bass- P.I of EPC.)
Agency for Health Care Quality and Research
Role: Advisor (5% effort)

To develop an instrument for attacks on health workers. 2012-2013
PI (Len Rubenstein)
US Institute of Peace
Role: Co-investigator (10% effort)

To develop an instrument for attacks on health workers. 2012-2013
PI (Len Rubenstein)
McArthur Foundation $434,782
Role: Co-investigator (15% effort)

To conduct a benefit and harm assessment of *roflumilast* in COPD. 2012-2013
Johns Hopkins ICTR
Role: Co-investigator (5% effort)

To develop a China-JHU consultation for civil society public health professionals. 2012
Open Society Foundation $49,534
Role: PI (20% effort). Proposal for a public health training program.

PACER. 2012
PI (Rothman)
Google-Flu
Role: Coinvestigator (5%) Systematic reviewer and meta-analysis expert.

Methods for Balancing Benefits and Harms in Systematic Reviews
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $188,871
Role: Project Task Leader and co-Investigator (10% effort)

Comparative effectiveness review of Meditation Programs for Stress and Wellbeing
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $375,666
Role: Project Task Leader and co-Investigator (15% effort)

Comparative effectiveness review of prevention of VTE in special populations
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $375,666
Role: Project Principal Investigator (20% effort)

To prevent and respond to gender-based violence (GBV) in refugee and conflict-affected populations. 2010-2011
(PI, Vu & Rubenstein) $293,946
Role: Co-investigator (10% effort)

Comparative effectiveness review of oral hypoglycemic medications
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2009-2010
AHRQ $125,000
Role: Co- Investigator (0% effort)

Johns Hopkins Clinical Research Junior Faculty Award. 2009-2012
NIH-KL2
ICTR
Role: Recipient (75% salary support)

Measuring exposure to human rights violations among men who have sex with men.
(PI, Mullany). 2009-2010
Center for Global Health Johns Hopkins $50,000
Role: Co-investigator (0% effort).

Research ethics for conducting research in vulnerable populations and unstable settings.
(PI, Mills) 2007-2009
CIHR $99, 887
Role: Co-investigator (10% effort).

Patents None.

Editorial work

Editor-in-chief and founder
BMC Conflict and Health 2007-12

Editorial Board Membership
Evidence Based Medicine (BMJ Group of Journals) 2017-current
Drug Safety 2008-16
American College of Physicians-PIER

Grant review 2012-current
Medical research foundation of New Zealand
Johns Hopkins Center for Public Health and Human Rights
Junior Faculty Research Grants
Medical Research Council of South Africa
Catalina Health Technology Assessment, Spain
Diabetes, UK
Johns Hopkins Medicine Research Council Synergy Awards
Johns Hopkins Institute for Clinical and Translational Research

Peer Review

1. *Acta Diabetologica*
2. *American Heart Journal*
3. *American Journal of Addictions*
4. *American Journal of Cardiovascular Drugs*
5. *American Journal of Managed Care*
6. *American Journal of Psychiatry*
7. *Annals of Internal Medicine*
8. *Annals of Medicine*
9. *Australian Medical Journal*
10. *BMJ*
11. *BMC Clinical Pharmacology*
12. *British Journal of Clinical Pharmacology*
13. *Bulletin of the World Health Organization*
14. *Chest*
15. *Circulation*
16. *Canadian Medical Association Journal*
17. *Clinical Pharmacology and Therapeutics*
18. *Clinical Trials*
19. *Cardiovascular Drugs & Therapy*
20. *Cochrane Collaboration*
21. *Disasters*
22. *Diabetolgia*
23. *Drug and Alcohol Dependence*
24. *Diabetes Obesity and Metabolism*
25. *Drug Safety*
26. *Epidemiology*
27. *European Journal of Neurology*
28. *European Journal of Pharmacology*
29. *European Respiratory Journal*
30. *Expert Opinion in Drug Safety*
31. *Global Public Health*
32. *Health Policy*
33. *International Journal of Epi*
34. *International Journal of Obesity*

35. Journal of the American College of Cardiology
36. Journal of the American Medical Association (5 in last 12 mo)
37. Journal of the American Medical Association-Internal Medicine
38. Journal of Cardiac Failure
39. Journal of Medical Case Reports
40. Journal of the Pancreas
41. Journal of General Internal Medicine
42. Medscape General Medicine
43. Medical Journal of Australia
44. Nephrology Dialysis Transplantation
45. North Carolina Medical Journal
46. Nutrition, Metabolism & Cardiovascular Diseases
47. Pediatric Infectious Disease Journal
48. Pharmacoepidemiology & Drug Safety-Best Reviewer Award 2013
49. Public Library of Science Medicine
50. Primary Care Respiratory Journal
51. Pediatrics
52. Research Synthesis Methods
53. Respiratory Medicine
54. Respirology
55. Southern Medical Journal
56. The Lancet
57. Thorax
58. Tropical Medicine & International Health

Abstracts and Presentations

Oral Presentations

National/International

1. GLP-1-based therapies and risk of pancreatitis: A matched case-control study. 29th International Society of Pharmacoepidemiology, Annual Meeting, Montreal Convention Center, August 26. Montreal, Quebec, Canada.2013
2. GLP-1 based therapies and risk of pancreatitis. 36th SGIM Annual Meeting, Denver, Colorado Posters. 2013
3. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomized controlled trials and observational studies, Society of General Internal Medicine, Minneapolis, Minnesota. 2011

4. Odds of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of clinical trials and observational studies, 27th International Society of Pharmacy-Epidemiology, Annual Meeting, Hyatt Regency August 24th. Chicago, Illinois. 2011

Local/Regional

Not applicable

Posters

National/International Meetings

1. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review 2018. International Society of Pharmacoepidemiology, Prague, August 24, 2018.
2. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. Health Care Systems Research Network, San Deigo, March 22, 2017.
3. GLP-1 based therapies and risk of pancreatitis. Pancreatitis, Diabetes, and Pancreatic Cancer Workshop. NIH, Bethesda, Maryland. 2013
4. Thiazolidinediones and risk of bladder cancer: A systematic review and meta-analysis. 36th SGIM Annual Meeting, Denver, Colorado.2013
5. Who is the patient's doctor? Primary care responsibility and co-management relationships among generalist and non-generalist physicians in the National Ambulatory Care Survey, 2002 SGIM 29th Annual Meeting, Los Angeles, California.2006
6. The educational value of case reports from the SGIM national meeting in the internal medicine clerkship. SGIM 29th Annual Meeting, Los Angeles, California.2006
7. Using IPod technology to create a self-guided clinic tour for resident orientation SGIM 29th Annual Meeting, Los Angeles, California.2006
8. Narcotic management in chronic non-malignant pain. A survey of resident's knowledge and attitudes. SGIM 29th Annual Meeting, Los Angeles, California.2006
9. Formulary conversion programs pose a significant risk to patients, SGIM 27th Annual Meeting, Chicago, Illinois.2004

Local regional meetings

Inhaled corticosteroids and the risk of fractures in COPD: A systematic review and meta-analysis. DOM Annual retreat, Johns Hopkins University 2011

Invited presentations

National/International

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. NIH Collaboratory Grand Rounds [Web] March 2, 2018
2. Resurgence of hepatocellular carcinoma in the era of oral direct acting antivirals. Cause or Consequence? Fundamentals of Biomedicine Seminar Series. Texas Tech University Health Sciences Center. El Paso, Texas Dec 13, 2017

3. Aligning evidence with preferences: Methodological Challenges and Opportunities. - Department of Medicine. Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
    - Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
    - Department of Health Services and Research, Michael De-Bakey VA and Baylor University, Houston, Texas, May 16, 2016.
    - Meyers Primary Care Institute and Department of Family and Community Medicine, University of Massachusetts, Massachusetts, March 31 and June 9 2016.
    - VA Center for Chronic Disease and Outcomes Research, Minnesota VA, March 2016.
    - Department of Medicine. University of Central Florida, Orlando, Florida, November 2015.
    - Center for Health Policy and Research Grand Rounds. UC Davis, Sacramento California, Oct 9 2015;
    - Center for Evidence and Outcomes, Agency for Health Care Research and Quality. Gaithersville Maryland, August 31, 2015.
4. Risks of Spiriva Respimat outweigh its benefit: A Debate. Inhalation Asia, University of Hong Kong, Department of Pharmacology and Pharmacy, Hong Kong. 2013
5. GLP-1-based therapies and risk of pancreatitis. Center for Clinical Epidemiology and Biostatistics Seminar Series, Philadelphia, Pennsylvania. 2013
6. Visiting Professor. Department of Medicine. University of Alabama. 2013
7. Value based health care: Can shared decision making methods get us there? Center for Value and Effectiveness, Medicine Institute, Cleveland Clinic, Noon Conference.2013
8. Role of Multi-criteria decision analysis in regulatory policy
    - Stanford Prevention Research Center, Stanford University, Palo Alto, Stanford, California. 2013
    - South Carolina College of Pharmacy, Columbia, South Carolina.2013
    - Department of Medicine. UC Davis, Sacramento, California.2013
    - Department of Clinical Sciences, UT Southwestern, Dallas, Texas.2013
    - Department of Medicine, Geisenger Medical Center, Danville, Pennsylvania. 2013
9. Weighing benefits and risks: Role of shared decision making in type 2 diabetes. CTSA Grand Rounds, Mayo Clinic, Rochester, Minnesota. 2013
10. Are long-acting muscarinic agents safe for patients with COPD: A Debate. Airway Vista, Asan Medical Center, Seoul, Korea
11. Academia and industry collaboration for cardiovascular risk mitigation. CBI and Applied Clinical Trials. 6th Annual Summit, Closing Address. Ritz Carlton, Arlington, Virginia.2012
12. Varenicline: Where are we today? Tobacco Disease Research Program, UCSF. San Francisco California. Varenicline debate.2012
13. The Maoist Insurgency in Nepal: Health Systems Challenges and Opportunities Conference on Health in Fragile States: Challenges for the Next Decade. United States Institute of Peace. Washington DC.2011

14. Standards of Care and the Role of Community Advocacy in Clinical Trials. Clinical Research in Developing Countries, IIIrd Annual Marcus Evans Conference, Washington, DC.2008
15. Nepal-A Case study. Integrating public health methods into Conflict Analysis. Norman Patterson School of International Affairs, Carleton University, Ottawa, Canada.2007

Local/Regional

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. Research Seminar Series, Department of Family Medicine and Community Health. University of Massachusetts Medical School. June 15.2018
2. Safety of novel anticoagulants vs warfarin- a case study using complementary study designs. Quantitative Health Sciences, University of Massachusetts Medical School, February 28, 2017
3. GLP-1-based therapies and risk of pancreatic adverse events. University of Maryland, Division of Endocrinology, Metabolism and Nutrition, Grand Rounds, Baltimore, Maryland. 2013
4. Thiazolidinediones and Patient-Oriented Outcomes in Type 2 Diabetes, GIM Grand Rounds. Johns Hopkins University School of Medicine. 2012
5. Patient-Centered Benefit and Risk Assessment. Center for Health Services and Outcomes Research. Johns Hopkins University 2012
6. Varenicline and cardiovascular and neuropsychiatric adverse events: Do benefits outweigh risks? Welch Center Grand Rounds. Johns Hopkins University. 2011
7. The new wave, HIV, Human Rights and Men who have Sex with Men in Nepal. Johns Hopkins Bloomberg School of Public Health, 2011.
8. Network Meta-analysis and Serious Adverse Events. Network Meta-Analysis Methods Workshop. Johns Hopkins Bloomberg School of Public Health. 2010
9. Thiazolidinediones and Cardiovascular Outcomes in Type 2 Diabetes. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2008
10. How Safe Are Our Drugs and How Do We Know? North Carolina ACP, Durham.2008
11. Clinico Pathologic Conference. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
12. Globalization and Health Equity: An emerging Challenge for Academic Medicine. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
13. Thiazolidinediones and Cardiovascular Disease: The Seduction of Common Sense. Epidemiology Seminar Series, Public Health Sciences. Wake Forest University 2007

Workshops and Precourses

1. ISPOR National Meeting, Next Generation Comparative Effectiveness Research- Are we getting organized to facilitate research for the individual patient? Washington, DC May 24, 2016 (workshop)
2. SGIM national meeting, developing high-quality search strategies for systematic reviews. 2010
3. SGIM national meeting, Systematic Review. 2009

Peer reviewed original research publications (reverse chronological order)

Trainees *

1. **Singh S**, Fouyazi H, Anzuoni K, Goldman L, Min JY, Griffin M, Grijalva CG, Morrow JA, Whitmore C, Leonard CE, Selvan M, Nair V, Zhou Y, Toh S, Petrone A, Williams J, Fazio-

Eynullayeva E, Swain R, Cole DT, Andrade S. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review. Drug Safety 2018 (accepted)

2. **Singh S,** Zeiman S, Alan Go, Fortmann S, Wenger N, Fleg JL, Radziszewska B, Stone NJ, Zoungas S, Gurwitz J. Statins for Primary Prevention in Older Adults – Moving toward Evidence-Based Decision-Making. *J Am Geriatr Soc. 2018 Oct 2. doi: 10.1111/jgs.15449. [Epub ahead of print]*
3. Tisminetzky M, Nguyen HL, Gurwitz J, McManus D, Gore J, **Singh S**, Yarzebski J, Goldberg RJ. Magnitude and impact of multiple chronic conditions with advancing age in older adults hospitalized with acute myocardial infarction. *International Journal of Cardiology. Published* Online: August 22, 2018. https://doi.org/10.1016/j.ijcard.2018.08.062.
4. Chang HY, **Singh S**, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter-2 (SLGT-2) Inhibitors and Lower Extremity Amputation: A Retrospective Cohort Study. JAMA Internal Medicine 2018. 10.1001/jamainternmed.2018.3034 http://dx.doi.org/10.1001/jamainternmed.2018.3034. August 13, 2018
5. Birring SS, Kavanagh JE, Irwin RS, Keogh K, Lim KG, Ryu JH; **CHEST Expert Cough Panel**. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. Chest. 2018 Jul 20. pii: S0012-3692(18)31075-4. doi: 10.1016/j.chest.2018.06.038. [Epub ahead of print]
6. **Singh S**, Nautiyal A, Loke YK. Oral Direct-acting antivirals and the incidence or recurrence of hepatocellular carcinoma: a systematic review and meta-analysis. Frontline Gastroenterology Published Online First: 30 July 2018. doi: 10.1136/flgastro-2018-101017
7. Chang AB, Oppenheimer JJ, Rubin BK, Weinberger M, Irwin RS; **CHEST Expert Cough Panel**. Chronic Cough Related to Acute Viral Bronchiolitis in Children. Chest. 2018 Apr 26. pii: S0012-3692(18)30632-9. doi: 10.1016/j.chest.2018.04.019. [Epub ahead of print]
8. Haar RJ, Risko CB, **Singh S,** Rayes D, Albaik A, Alnajar M, et al. (2018) Determining the scope of attacks on health in four governorates of Syria in 2016: Results of a field surveillance program. PLoS Med 15(4): e1002559. https://doi. org/10.1371/journal.pmed.1002559
9. Pradhan R, * **Singh S.** Comparison of data on Serious Adverse Events and Mortality in ClinicalTrials.gov corresponding journal articles and medical reviews: A cross-sectional analysis. Drug Safety 2018 Apr 11. doi: 10.1007/s40264-018-0666-y. [Epub ahead of print]
10. Wu CH, Tu ST, Chang YF, Chan DC, Chien JT, Lin CH, **Singh S**, Dasari M, Chen JF, Tsai KS. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. Bone. 2018 2018 Jun; 111:92-100. doi: 10.1016/j.bone.2018.03.018. Epub 2018 Mar 16
11. Field SK, Escalante P, Fisher DA, Ireland B, Irwin RS; **CHEST Expert Cough Panel**. Cough Due to TB and Other Chronic Infections: CHEST Guideline and Expert Panel Report. Chest. 2018 Feb;153(2):467-497. doi: 10.1016/j.chest.2017.11.018. Epub 2017 Nov 28.
12. Erkskine NA, *Tran H, Levin LL, Ulbricht CM, Fingeroth JD, Kiefe CI, Goldberg RJ, **Singh S.** A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. PLoS One 2017 Jul 27;12(7): e0181565
13. **Singh S**. Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis of observational studies. American Journal of Medicine 2017;130(12):1449-1457

14. Marimuthu S, Iyer G, * Segal JB, **Singh S**. Patient-relevant outcomes associated with generic tamsulosin, levothyroxine, and amphetamine in the FAERS: A pilot study. J Comp Eff Res. 2017;6(5):437-447.
15. Iyer G, *Marimuthu S, *Segal JB, **Singh S**. An algorithm to identify generic drugs in the FDA Adverse Event Reporting System. Drug Safety 2017 2;40(9):799-808.
16. Tang W, *Chang HY, *Zhou M, * **Singh S**. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. *Sci Rep* 2017 Jan 20; 7:40120. doi: 10.1038/srep40120.
17. Onasanya O, Iyer G, * Lucas E, Lin D, **Singh S**, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 ;4(11):943-956
18. **Singh S**, Wright EE, Kwan AY, Thompson JC, Syed IA, Korol EE, Waser NA, Yu MB, Juneja R. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19(2):228-238
19. Alexander GC, Iyer G, Lucas E, Lin D, **Singh S**. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 ;130(3):293-305
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None

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Correspondence

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Development of major curricular offerings.

2 credit Course for MD and MPH in comparative effectiveness research for the Johns Hopkins ICTR 2015-2016

Sonal Singh MD, MPH received his MD from Patna Medical College India (1999). He completed internal medicine residency training at Unity Health System, affiliate of Strong Memorial Hospital Rochester, NY. (American Board of Internal Medicine 2005) He obtained an MPH from Johns Hopkins Bloomberg School of Public Health (2008) and completed subsequent research training at the Johns Hopkins Hospital (2012) as a Junior Faculty Research Scholar supported by the National Institute of Health. He was the Associate Director for the Center for Drug Safety and core faculty Evidence Based Practice Center and the Center for Public Health and Human Rights at Johns Hopkins University. He has taught and held faculty appointments at Wake Forest University School of Medicine and Johns Hopkins University. He has received numerous awards including the Senior Scholarship Award from the Unity Health System (2005), Tinsley R Harrison Teaching Award for Education at Wake Forest University in 2007, Master Teacher Award at Wake Forest University (2008), Mid-Atlantic Society of General Internal Medicine Clinician Investigator of the Year Award (2010), the Bruce P Squires Award for the best research paper of the year from the Canadian Medical Association Journal (2011) and the third best student abstract award from the International Society of Pharmacoepidemiology (2013). He conducts clinical research with a focus on evidence synthesis, drug safety and shared decision making. Dr Singh has conducted research in several countries and has published more than 150 academic manuscripts to advance research and clinical care. His research efforts have been supported by the NIH, FDA, Agency for Health Care Research and Quality and the Patient Centered Outcome Institute and various private foundations. His research has been published in *Science, NEJM, Journal of the American Medical Association, Annals of Internal Medicine, Lancet and the British Medical Journal*, and featured in various outlets including Nature Medicine, NYTIMES, CNN, Washington Post and the Wall Street Journal. He currently serves on the editorial board of the *Evidence Based Medicine Journal* published by the BMJ, as a panel member of the American College of Chest Physician guideline writing group, and American College of Physicians Health Policy committee (Massachusetts chapter) He has served as a consultant to the World Bank, World Health Organization International Agency for Research Cancer, the Agency for Health Care Research and Quality, pharmaceutical sponsors and research firms and several non-governmental organizations. He is a practicing general internist with a passion for managing patients with complex medical conditions.

EXHIBIT B

Trial Testimony

I have not provided trial testimony.

Expert deposition (last 5 years)

1. US District Court of South Carolina, Charleston; *In Re Lipitor (Atorvastatin Calcium) marketing, sales practices and products liability litigation*, MDL No. 2:14-mn-02502-rmg, April 28, 2015; supplementary deposition, in 2016.
2. US States District Court, Eastern District Court of California; *Kristi Lauris Individually and as Successor in Interest to the Estate of Dainis Lauris; vs Defendants Novartis AG*, Case No. 1:16 cv 00393 –LJO-SAB. Case 2:17-cv-14302-RLR Document 49 Entered on FLSD Docket, 2017.
3. Circuit Court of Camden County, Missouri; *Grace Arlene Rahmoeller v. Walmart Stores, Inc. and Nicholas B. Collins*, Case No.: 15CM-CC00238, April 16, 2018.
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